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Efficacy of ginger (*Zingiber officinale*) in ameliorating chemotherapy-induced nausea and vomiting and chemotherapy-related outcomes: a systematic review update and meta-analysis

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MC led the design, implementation, data analysis and drafting of the manuscript. SM duplicated data extraction and GRADE assessment. WM duplicated risk of bias assessment and GRADE assessment. All authors contributed to study concept and revision of the manuscript. MC completed this work in partial fulfilment of her PhD candidature.

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Declaration of conflicting interests

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Research Snapshot

Research Question: This systematic review update with meta-analyses, in adult cancer patients receiving chemotherapy, aims to determine: what are the effects of ginger supplementation dose and duration on the incidence and severity of chemotherapy-induced nausea and vomiting (CINV) and outcomes related to CINV (e.g. quality of life, fatigue, adverse events), compared to placebo or standard anti-emetic medication?

Key Findings: Eighteen papers were analysed. The likelihood of acute vomiting was reduced by 60% with ginger supplementation of ≤1g/day for >3-days duration, compared to control groups (OR: 0.4; 95% CI: 0.17-0.81; P=0.01). The likelihood of fatigue was reduced by 80% with ginger supplementation of any dose for <3-days duration (OR: 0.2; 95% CI: 0.03-0.87; P=0.03). No statistically significant association was found between ginger and likelihood of overall or delayed vomiting, likelihood or severity of nausea, or other outcomes related to CINV.

Abstract

Background: Ginger has been proposed as an adjuvant treatment for chemotherapy-induced nausea and vomiting (CINV).

Objective: The aim of this systematic review with meta-analyses is to evaluate, in adult cancer patients receiving chemotherapy, the effects of ginger supplementation dose and duration on the incidence, duration, and severity of CINV and outcomes related to CINV (quality of life, fatigue), compared to placebo or standard anti-emetic medication.

Method: Five electronic databases were searched from database inception to April 2018. The quality of evidence was appraised with the Cochrane Risk of Bias tool and GRADE. Data were pooled using Revman.

Results: Eighteen papers were analysed. The likelihood of acute vomiting was reduced by 60% with ginger supplementation of ≤1g/day for >3-days duration, compared to control groups (OR: 0.4; 95% CI: 0.17-0.81; P=0.01; n=3 studies; n=3 interventions; n=301 participants; I^2=20%; GRADE level: moderate). The likelihood of fatigue was reduced by 80% with ginger supplementation of any dose for <3-days duration (OR: 0.2; 95% CI: 0.03-0.87; P=0.03; n=1 studies; n=2 interventions; n=219 participants; I^2=0%; GRADE level: low). No statistically significant association was found between ginger and likelihood of overall or delayed vomiting, likelihood or severity of nausea, or other outcomes related to CINV.

Conclusions: Ginger supplementation might benefit chemotherapy-induced vomiting as well as fatigue. Due to clinical heterogeneity, this systematic review update found no association between ginger and chemotherapy-induced nausea and other CINV-related outcomes. The results of this systematic review and meta-analysis provide a rationale for further research with stronger study designs, adequate sample sizes, standardized ginger products, and validated outcome measures to confirm efficacy of ginger supplementation and optimal dosing regimens.

Introduction

Nausea and vomiting are among the most distressing side effects of chemotherapy (CTx).[1,2] Chemotherapy is a common and effective treatment for cancer; however, chemotherapy-induced nausea and vomiting (CINV) can affect treatment completion as it is known to exacerbate fatigue, anxiety and depression,[3] as well as decrease quality of life (QoL) and food intake.[4-7] Consequently, CINV is attributable to 50-60% of CTx patients experiencing protein-energy malnutrition as a result of failing to meet nutritional requirements,[8] which further compromises treatment outcomes.[9] Good management of CINV is therefore a priority to optimize treatment efficacy, QoL, and subsequent survival.[4-6]

Anti-emetics to prevent and manage CINV are often prescribed in combination, with the precise regimen tailored to the emetogenicity of the CTx and patient characteristics.[10] Consensus between the three main clinical guidelines for anti-emetic prescription suggests the administration of a serotonin ($5\text{-}HT_3$) receptor antagonist and dexamethasone for moderately emetogenic CTx regimens (those with 30-90% risk of emesis), with the addition of a neurokinin 1 (NK_1) receptor antagonist for patients receiving highly emetogenic CTx (>90% risk of emesis).[11,12] Despite pharmacological developments with combination anti-emetics, CINV remains a problematic side effect of CTx.[13]

Ginger (*Zingiber officinale*) is a traditional remedy for nausea and vomiting in many cultures and has been investigated for use in motion sickness, morning sickness, and post-operative nausea.[14] More novel is the role of ginger for the prevention and management of CINV.[15,16] The exact mechanism remains unclear; however, beneficial effects are thought to be due to the effects of gingerol and shogaol compounds on multiple components of CINV pathways.[17] The most well understood pathway is ginger's antagonistic effect on $5\text{-}HT_3$ receptors. Ginger non-competitively inhibits $5\text{-}HT_3$ receptor activation in humans via binding at a site that is different from other types of $5\text{-}HT_3$ receptor antagonists.[18] Therefore, synergistic inhibition of $5\text{-}HT_3$

signalling might occur when ginger is combined with other 5-HT_3 antagonists, for example ondansetron, a common anti-emetic administered during CTx, suggesting there are additional beneficial effects when ginger is included in anti-emetic regimens.[17,19] Ginger is also thought to render beneficial effects through its antagonistic effect on muscarinic and histaminergic receptors; its ability to regulate gastric emptying and gastrointestinal motility; and its role in reducing oxidative stress and inflammation.[17] These multiple pathways may also be linked with other CINV-related symptoms such as fatigue, anxiety, and depression, thereby impacting overall health-related quality of life.[3,17,20-22]

Two systematic reviews, both published in 2013,[15,16] explored the effect of ginger on CINV. The first review identified seven clinical studies that investigated supplemental ginger to treat CINV.[15] Qualitative examination of included studies was used by Marx et al.[15] to conclude that the available literature provided mixed support for the use of ginger, not warranting standard recommendations for its use in the clinical setting. The second review identified five double-blind placebo-controlled randomized trials for inclusion, and meta-analysis determined no significant association between ginger and the control of CINV.[16] However, both reviews highlighted major limitations in existing research in terms of study design with non-standardized CTx and anti-emetic regimens, inconsistent and/or inadequate ginger intervention dose and duration, as well as failure to identify or control potentially confounding variables.[15,16]

Due to the inconclusive nature of the previous systematic reviews[15,16] and more recent publication of clinical trials that examine the effect of ginger on CINV, an updated review of the literature was warranted. The aim of this systematic review update with meta-analyses was to evaluate, in adult cancer patients receiving CTx, the effects of ginger supplementation dose and duration on the incidence and severity of CINV and outcomes related to CINV (quality of life, fatigue), compared to placebo or standard anti-emetic medication.

Method

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[23] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO number: CRD42017077022).

Search Strategy

PubMed, the Cochrane Library, and CINAHL databases were previously searched by the authors from database inception up until April 2012 to locate both parallel and crossover intervention trials. The findings of that search were reported by Marx et al.[15] For this update, these databases were searched to locate studies published from April 2012 to April 2018 with the addition of two databases: Embase and Web of Science, which were searched from database inception to 19 September 2017. The search strategy used for this updated review was similarly based upon the following terms: (ginger* OR zingiber officinale) AND (cancer* OR chemotherap*) AND (nausea OR vomit*) AND (randomized controlled trial OR intervention). The search strategy was designed in PubMed using a combination of keywords and controlled vocabulary and translated to other databases with Polyglot[24] (full search strategy is shown in Online Supplementary Material 1). A snowballing search was also used, whereby reference lists of included studies and previous systematic and narrative reviews were considered to identify additional studies not found in the systematic search strategy up until 4 April 2018. Initial screening of titles and abstracts, as well as full-text screening, were completed by two investigators independently (MC and SM). Disagreement between reviewers was resolved by discussion with a third researcher (WM).

Selection of studies

Studies published in any language were included in this review if they provided an intervention

of ginger supplementation in any form to adult (mean sample age ≥18 years) human participants undergoing CTx for cancer and had used a control of either placebo or anti-emetic medication. Studies were excluded if the population of interest was receiving concurrent radiation therapy, which is a known predictive factor for nausea and vomiting. Studies were included if participants were undergoing other therapies such as surgery, biologics, immunotherapy, and bone marrow transplant therapy. Non-English language studies were also excluded if they could not be translated to English with Google Translate software.[25] The primary outcomes of interest were CINV incidence (number of participants who reported nausea and/or vomiting of any severity) and nausea severity (measured using any tool). Secondary outcomes were patient QoL, fatigue, anxiety or depression, adverse events (any reported side effects relatable to the intervention), adherence to the intervention, stomach dysrhythmia, tachygastria or bradygastria, nutritional status, dietary intake, health service use, health care costs, and mortality.

Data extraction and review of study quality

Data extraction and individual study quality assessment using the Cochrane Risk of Bias Tool[15] were carried out independently on all studies, including eligible studies identified in the review by Marx et al., by two authors (MC and [WM or SM]), with disagreements managed by consensus.

The certainty in the body of evidence for each outcome of interest was classified by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[26] with the software GRADEpro GDT [GRADEpro Guideline Development Tool, McMaster University, 2015 (developed by Evidence Prime, Inc)]. Four levels of certainty for the estimated effect were utilized by the GRADE assessment: very low (very little confidence), low (limited confidence), moderate (moderately confident), and high (very confident). The

GRADE level of evidence was determined by review and discussion amongst three authors (MC, SM, and WM).

Meta-analysis

Where two or more interventions reported the same outcome with sufficient incidence or mean and variance data, outcomes for the intervention and control group were pooled by meta-analysis using Revman.[27] The overall effect size was calculated by combining all the individual studies' outcome data and associated 95% confidence interval (CI) to calculate an odds ratio or mean difference using the standard random effects method in Revman. The pooled categorical outcomes were reported as odds ratios (OR; ratio of the odds of the outcome in the two groups of interest) with 95% confidence intervals, using the Mantel-Haenszel test. The inverse variance test pooled continuous outcomes, which were reported as mean differences (MD) where the same tool and scale was used, or the standardized mean difference (SMD) where different measurement scales or tools for the same construct were used. To support clinical interpretation, SMDs were re-expressed into a scale of one of the included measurement tools by multiplying the SMD effect size by the standard deviation of the tool's scale in the total sample.[28] Heterogeneity was evaluated with the I^2 statistic, with >50% representative of substantial heterogeneity.[29] A P value of less than 0.05 was considered the cut off for statistical significance. When meta-analyses included 10 or more studies, a funnel plot was generated by Revman to assess publication bias. If there was a non-significant trend or substantial heterogeneity, sensitivity analyses were undertaken with study factors such as participant characteristics, study design, study quality, and intervention/confounding variables. Additionally, to identify the effect of various dosing regimens, subgroup analyses were performed. Due to conflicting optimal dosing regimens and duration of intervention in the literature, interventions were divided as evenly as possible which generated the daily dosing categories of ≤1g / >1g and duration categories of ≤3 / >3 days. Therefore, subgroup analyses

were undertaken using four groups: 1) short intervention duration (≤3 days per CTx cycle) with low dose (≤1g/day); 2) short intervention duration (≤3 days per CTx cycle) with high dose of ginger (>1g/day); 3) long intervention duration (>3 days per CTx cycle) and low dose of ginger (≤1g/day); 4) long intervention duration (>3 days per CTx cycle) and high dose of ginger (>1g/day). Additionally, it was hypothesized that ginger could have varying levels of efficacy for anticipatory (prior to CTx), acute (≤24 hours post CTx), and delayed (>24 hours post CTx) CINV; therefore, separate analyses were performed for each.

Results

Search results and study quality

The search strategy and study selection process that led to the 18 studies included in this review are displayed in Figure 1. A total of 13 papers were analysed in nine meta-analyses. Figure 2 indicates that risk of bias across all papers was mostly low, with all but four papers included having low risk of bias for at least four of the seven domains (justifications are shown in Online Supplementary Material 2). However, the majority of papers had an unclear or high risk of bias for allocation concealment, mainly due to papers failing to provide a description of concealment procedures. Two papers,[30,31] which reported nausea outcomes only, had poor study quality due to >70% of Cochrane Risk of Bias domains rated as unclear or high risk of bias. Due to the small number of studies in each meta-analysis, publication bias could not be assessed.

Intervention characteristics

Characteristics of the 18 included studies are summarized in Table 1 and shown in detail in Online Supplementary Material 3. Konmun et al.[32] and Danwilai et al.[33] reported different outcomes in each paper; however, they refer to the same study and intervention. One study had two intervention arms[34] and another had three intervention arms;[35] therefore, a total of 20 interventions are referred to in this review.

The active constituents in the ginger interventions were specified in ten interventions. Combined gingerols, zingerone, and shogoals of an unspecified dose were used in three interventions;[35] gingerols (ranging from 11-16 mg) and shogoal (ranging from 0.92-1.12 mg) were used in four interventions;[34,36-38] and gingerols (ranging from 0.5-150 mg) alone were administered in three interventions.[32,33,38,39] Adherence to the prescribed supplements ranged from 71%[39] to 97%[40] with no significant difference between intervention and control groups.

Study samples

Sample sizes ranged from n=20[41] to n=375[35] (n=1,652 total participants; 64% female) and are reported in detail in Online Supplementary Material 3. Participants in eight studies were administered platinum-based CTx with or without other CTx agents,[32,33,36,38,42-45] six were administered anthracycline-based CTx,[31-33,40,45,46] and six studies did not specify the CTx agents administered to participants.[30,34,35,37,39,47] Six studies reported patients received single-day CTx treatments,[34,36,37,39,47] while the remaining studies did not specify days of CTx treatment. Participants in 13 studies were administered a corticosteroid in combination with a 5-HT_3 receptor antagonist;[31-33,35-37,40-44,46,47] and seven were administered additional anti-emetics.[31,32,36,40,43,44,47]

Efficacy of ginger supplementation for nausea and vomiting outcomes

Table 2 contains all meta-analyses conducted for primary and secondary outcomes. Forest plots for all non-significant meta-analyses are shown in Online Supplementary Material 4 and justifications for the all GRADE levels are shown in Online Supplementary Material 5. In terms of primary outcomes, the only significant finding was for duration of >3 days of supplementation with doses ≤1g/day which reduced the likelihood of acute vomiting by 60% (Figure 3). Results regarding anticipatory CINV were unable to be pooled due to lack of studies that reported this outcome. Only one study reported results related to anticipatory nausea,

finding no significant difference in likelihood of anticipatory nausea between control and intervention groups.[36] However, it is unclear whether participants in this study were consuming the intervention at the time of anticipatory nausea being measured (at day 21 or 28 prior to commencing subsequent CTx cycles). Only one study reported results related to anticipatory vomiting, which found significantly higher incidence among the control group compared to those who received ginger supplementation (IG n=0.5/40 (SD 0.3); CG n=1.5/40 (SD 5.9); P=0.04).[37]

In terms of secondary outcomes, three of the four studies[32,38,39] that reported data on QoL found a statistically significant difference in QoL scores between control and intervention groups at the end of the study period, favouring ginger intervention over control, however, no significant association was found with meta-analysis (Table 2). The only significant findings in regards to fatigue were identified with sensitivity analysis, which found ginger supplementation of any dose for ≤3-days reduced likelihood of fatigue by 80% (Figure 4). No studies reported outcomes on anxiety and depression; stomach dysrhythmia, tachygastria or bradygastria; nutrition status; dietary intake; health service use; or health care costs.

Seven studies reported on events believed to be directly attributable to the intervention.[33,35-39,43] Of these, three provided adequate data for meta-analysis, finding ginger supplementation of any dose for any duration significantly increased likelihood of any gastrointestinal, flushing, rash-related, or unspecified adverse event (Figure 5). Reported gastrointestinal symptoms potentially relatable to the study intervention included dry mouth, heartburn, reflux, constipation and diarrhoea; however, due to insufficient data for meta-analysis, only the results on heartburn were able to be pooled, finding no association between ginger supplementation of any dose for any duration and likelihood of heartburn. Studies reported no significant differences between adverse events not directly attributable to the intervention, which included neutropenia and other unspecified biochemical markers, restlessness, headache, and heart

palpitations. Two studies reported incidence of mortality, with no statistically significant difference reported between intervention and control groups.[44,45]

Discussion

This systematic review update with meta-analyses provides the most current and comprehensive meta-analysis to date exploring the use of ginger for CTx patients. Consistent with conclusions made in the previous two systematic reviews on the topic,[48,49] ginger supplementation in conjunction with standard anti-emetic care could be beneficial for CTx-induced vomiting and CINV-related outcomes. Although there is low to very low certainty in the estimated effect size, ginger supplementation is suggested to have large beneficial effects on likelihood of acute vomiting, as well as small but significant improvements on fatigue among individuals receiving CTx. Findings remain inconclusive as to whether ginger benefits delayed CTx-induced vomiting, CTx-induced nausea, and QoL.

Despite most papers that reported on nausea incidence favouring ginger supplementation over comparator interventions,[30,38,42,45,46,50] the pooled estimate found no association with no statistical heterogeneity (I^2=0%), therefore there is some confidence in this finding. However, meta-analyses results in regards to likelihood of nausea appear to be skewed by one larger study.[36] Therefore, ginger supplementation for improvements in nausea incidence cannot yet be disregarded as a treatment option due to the substantially large clinical heterogeneity between studies.

The non-significant finding which favoured control for nausea severity, particularly for delayed nausea severity when administered for ≤3-days, was driven by only two studies;[34,42] which were the only studies included in the model after sensitivity analysis. Although there was no statistical heterogeneity, there was substantial clinical, as well as only a small number of studies included which used a range of un-validated outcome evaluation questionnaires.

This review found low confidence that supplementation of ≤1g/day of ginger for >3-days, starting on Day 1 of CTx reduces likelihood of vomiting by 20-70%; where other dosing regimens were found to have no significant association. Uncertainty in regards to the ideal ginger dosage is likely due to the clinical heterogeneity. Ginger supplementation of ≤1g/day for >3-days potentially reduces likelihood of overall vomiting by 50% (OR: 0.5; 95% CI: 0.21-1.13) and delayed vomiting by 70% (OR: 0.3; 95% CI: 0.10-1.13); however, the results were not significant at $p<0.05$, likely attributable to significant clinical heterogeneity among included studies. The only statistically significant finding that ginger administration for >3-days benefited acute vomiting is conflicting, as only ginger consumed prior to and within the first 24-hours is applicable to acute symptoms (i.e. symptoms within the first 24 hours). This unlikely finding is further evidence of the impact of clinical heterogeneity leading to decreased confidence in the results, suggesting that until further well-designed studies with homogenous or well-controlled samples are available, all results should be considered with caution, including those with no statistical heterogeneity.

In terms of dosage frequency, research suggests ginger should be distributed at least four times across the day rather than once or twice daily due to ginger's short elimination half-life of ≤2 hours.[51] However, most studies in this review administered ginger only once or twice per day, which suggests the effects of ginger may be underestimated. Furthermore, the delivery method of ginger administered may also affect the half-life. Although the half-life of ginger is short, production of ginger-induced intestinal microbiota metabolites may be a suggested mechanism for reducing activation of CINV pathways.[17,52,53]

This was the first systematic review to explore additional CINV-related outcomes, finding that ginger resulted in beneficial effects outside of the direct CINV pathways. A decrease in fatigue was seen with ginger administration, a common and problematic symptom otherwise difficult to treat and manage.[54] The decrease may be due to ginger's proposed anti-inflammatory effects,

as inflammation is a pathway for fatigue,[17,20-22] however, none of the included studies examined inflammatory markers. Further studies are needed to build confidence in the body of evidence for the effect of ginger on other CINV-related outcomes.

Adherence to the intervention was found to be high overall and no different to placebo groups, implying that ginger supplementation as an additional medication is feasible and does not impose any additional factors which might prevent adherence. Although this review found ginger did not cause serious adverse events and therefore could be considered safe, it should be noted that there was poor reporting of adverse events in most studies as well as a failure to distinguish events reasonably relatable to the intervention. Although statistically significant results were obtained to suggest likelihood of adverse events is higher among individuals administered ginger, the adverse events were mild. Meta-analysis suggested that the likelihood of heartburn, a commonly reported side effect of ginger, did not differ between the study groups. Mortality, arguably the most serious adverse event, also did not appear to differ between study groups in the limited number of studies that reported this event.

Limitations in the literature

Although a substantial number of new studies were identified in this systematic review update, the included studies are clinically heterogeneous, which decreases confidence in the results and contributes to the large number analyses which had insufficient evidence to reject the null hypothesis. Sources of clinical heterogeneity were varying CTx and anti-emetic regimens as well as cancer types and participant samples. In addition, substantial clinical heterogeneity was introduced through lack of reporting of, or large variations across studies in ginger interventions; specifically, the composition of active constituents, dosing frequencies and delivery methods. Sensitivity analysis was able to be explored for study quality and overall ginger dosing regimens, but other sources of clinical heterogeneity could not be accounted for

and publication bias was not able to be assessed. Furthermore, this review was limited by the small number of available studies that reported the outcomes of interest.

Directions for future research

The results of this systematic review and meta-analysis provide a rationale for further research such as that which is currently underway.[55] In line with recommendations from the previous systematic review,[48] additional randomized controlled trials with adequate sample sizes, standardized ginger products, use of validated outcome measures, and full reporting of data would better inform the evidence regarding the type of ginger supplement that should be recommended and the most effective dosing schedule. Study designs should also measure adverse events potentially relatable to the ginger intervention to determine the safety of the intervention. Other CTx-related outcomes that are associated with CINV need to be assessed, including anxiety and depression, stomach dysrhythmia, and tachygastria or bradygastria. Other factors that need evaluation related to overall health include nutrition status, dietary intake, health service use, and health care costs. Patients receiving multi-day CTx regimens should be included in studies before recommending ginger products to all patients receiving CTx. The potential mechanisms of action of ginger having beneficial effects on CINV pathways also need investigation.

Conclusion

Ginger supplementation can potentially benefit CTx-induced vomiting as well as fatigue. Due to clinical heterogeneity, this systematic review update with meta-analyses found no association between ginger and CTx-induced nausea or other CINV-related outcomes. The results of this systematic review and meta-analysis provide a rationale for further research using stronger study designs, adequate sample sizes, standardized ginger products, and validated outcome measures to confirm efficacy of ginger supplementation and optimal dosing regimens.

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590 **Table 1.** Summary of intervention characteristics and study samples of the 18 included studies in this systematic review with meta-analyses aiming
591 to evaluate, in adult cancer patients receiving chemotherapy, the effects of ginger supplementation dose and duration on the incidence and severity
592 of chemotherapy-induced nausea and vomiting and outcomes related to chemotherapy-induced nausea and vomiting (quality of life, fatigue).

Citation	Country	Study Design	Sample Size	CTX emetogenicity	Anti-emetic Use (Yes/No)	Intervention	Intervention dose	Intervention duration	Comparator
Alparslan 2012 [30]	Turkey	Non-RCT	N=45	Not specified	Not specified	Tablet (ginger type unspecified)	1.6g/d (2x 0.4g BD)	Entire treatment duration	IV antiemetic
Arslan 2015 [31]	Turkey	RCT	N=60	Not specified	Yes	Sachet (powdered ginger root on yoghurt)	1g/d (0.5g BD)	3 days; from 30 mins before Cycle 1 Day 1	Standard care
Bossi 2017 [36]	Italy	Double blind placebo RCT	N=251	High	Yes	Capsule (liquid ginger root extract)	0.16g/d (2x 0.04g BD)	42-56 days; from Day 2 of each Cycle	Placebo
Danwilai 2017 [33]	Thailand	Pilot double blind placebo RCT	N=50	Moderate or high	Yes	Capsule (powdered ginger root extract)	0.02g/d (2x0.005g BD)	From 3 days prior to Cycle 1 Day 1 through to Cycle 4	Placebo
Fahimi 2011 [42]	Iran	Double blind crossover placebo RCT	N=50	Not specified	Yes	Capsule (powdered ginger root extract)	1g (2x 0.25g BD)	3 days; from Cycle 1 Day 1, then a 3-week washout period	Placebo
Konmun 2017 [32]	Thaliand	Double blind placebo RCT	N=88	Moderate or high	Yes	Capsule (type unspecified)	0.02g/d (2x0.005g BD)	From 3 days prior to CTx Day 1 for at least 3 Cycles	Placebo
Li 2018 [38]	China	Double blind placebo RCT	N=146	Moderate or high	Yes	Capsule (powdered ginger root extract)	0.5g/d (2x0.25g BD)	5 days; from CTx Day 1	Placebo
Manusirivithaya 2004 [43]	Thaliand	Double blind crossover RCT	N=48	High	Yes	Capsule (powdered ginger root extract)	1g (0.25g QID)	5 days; then a 3-4 week washout period	Placebo
Marx	Australia	Double blind placebo RCT	N=51	Not specified	Yes	Capsule	1.2g	5 days; from CTx Day 1	Placebo

2017 [39]						(powdered ginger root extract)	(0.3g QID)		
Montazeri 2013 [44]	Iran	Crossover double blind placebo RCT	N=44	Not specified	Yes	Capsule (powdered ginger root extract)	1g/d (2x 0.25g BD)	For one Cycle (at least 28 days) before crossing over	Placebo
Muthia 2013 [41]	Indonesia	Control time series	N=20	Not specified	Yes	Drink (type unspecified)	1 serve (QID)	Not specified	Standard care
Panahi 2012 [46]	Iran	Open pilot RCT	N=100	Moderate or high	Yes	Capsule (powdered ginger root extract)	1.5g (0.5g TID)	5 days; from CTx Day 1	Placebo
Ryan 2012 [35]	USA	Double blind placebo RCT	N=371	Any	Yes	Capsule (liquid ginger root extract)	0.5g/d (2x0.25g)	6 days; from 3 days before CTx Day 1	Placebo
			N=375	Any	Yes	Capsule (liquid ginger root extract)	1g/d (4x 0.25g)	6 days; from 3 days before CTx Day 1	Placebo
			N=375	Any	Yes	Capsule (liquid ginger root extract)	1.5g/d (6x 0.25g).	6 days; from 3 days before CTx Day 1	Placebo
Sanaati 2016 [47]	Iran	Double blind RCT	N=43	Not specified	Yes	Capsule (powdered ginger root extract)	1g/d (0.5g BD)	10 days; from 5 days before CTx Day 1	Standard care
Shokri 2017 [45]	Iran	Double blind placebo RCT	N=49	Not specified	Not specified	Capsule (type unspecified)	2g/d (1g BD)	For 6 Cycles	Placebo
Thamlikitkul 2017 [40]	Thailand	Double blind crossover placebo RCT	N=34	High	Yes	Capsule (powdered ginger root extract)	1g (0.5g BD)	5 days; from CTx Day 1	Placebo
Yekta 2012 [37]	Iran	Double blind placebo RCT	N=98	Any	Yes	Capsule (powdered ginger root extract)	1g (0.25g QID)	6 days; from 3 days before CTx Day 1	Placebo

Zick 2009 [34]	USA	Double blind placebo RCT	N=110	Any	Yes	Capsule (powdered ginger root extract)	1g/d (4x 0.25g)	3 days; from CTx Day 1	Placebo
			N=109	Any	Yes	Capsule (powdered ginger root extract)	2g/d (8x 0.25g)	3 days; from CTx Day 1	Placebo

593 CTX: chemotherapy; RCT: randomised controlled trial; IV: intravenous; BD: twice daily; QID: four times daily; TID: three times daily

594

595

Table 2. Results from meta-analyses conducted to evaluate, in adult cancer patients receiving chemotherapy, the effects of ginger supplementation dose and duration on the incidence and severity of chemotherapy-induced nausea and vomiting and outcomes related to chemotherapy-induced nausea and vomiting (quality of life, fatigue).

Outcome	Pooled estimate	Significance of pooled estimate	Heterogeneity (I^2)	Number of interven-tions	Sample Size	GRADE level
Nausea incidence						
Overall nausea incidence:[a] *any dose, any duration*	OR: 1.0, 95% CI: 0.74-1.28	P=0.82[b]	0%[c]	8	883	moderate
Acute nausea incidence: *any dose, any duration*	OR: 0.8, 95% CI: 0.47-1.42	P=0.47[b]	63%	6	590	very low
Delayed nausea incidence:[a] *any dose, any duration*	OR: 0.9, 95% CI: 0.65-1.30	P=0.64[b]	28%	7	834	moderate
Nausea Severity						
Overall nausea severity: *any dose, any duration*	SMD: 0.2, 95% CI: -0.02-0.38	P=0.08	0%[c]	3	378	low
Acute nausea severity: *any dose, any duration*	SMD: 0, 95% CI: -0.17-0.23	P=0.76[b]	0%	5	438	low
Delayed nausea severity: *any dose, any duration*	SMD: 0.4, 95% CI: -0.07-0.77	P=0.10[b]	75%	4	378	very low
Vomiting Incidence						
Overall vomiting incidence:[a] *any dose, any duration*	OR: 0.8, 95% CI: 0.44-1.36	P=0.38	66%	9	825	very low
Acute vomiting incidence: *any dose, any duration*	OR: 0.7, 95% CI: 0.38-1.24	P=0.22	57%	7	671	Very low
Acute vomiting incidence: *≤ 1g/day dose, >3 days duration*	OR: 0.4; 95% CI: 0.17-0.81	**P=0.01**	20%	3	301	moderate

Delayed vomiting incidence:[a] *any dose, any duration*	OR: 0.8, 95% CI: 0.39-1.79	P=0.63	76%	7	671	very low
Secondary Outcomes						
Quality of Life: *any dose, any duration*	SMD: 0.5, 95% CI: -0.07-1.01	P=0.09	78%	3	279	low
Fatigue Incidence: *any dose, any duration*	OR: 0.5, 95% CI: 0.13-1.61	P=0.22	60%	4	375	very low
Fatigue Incidence: *any dose, ≤3-days duration*	OR: 0.2, 95% CI: 0.03-0.87	**P=0.03**	0%[c]	2	219	Low
Adverse Events						
Heartburn incidence: *any dose, any duration*	OR: 1.9, 95% CI: 0.68-5.18	P=0.22	0%	3	312	low
Any gastrointestinal, flushing, rash-related, or unspecified adverse event: *any dose, any duration*	OR: 2.0, 95% CI: 1.39-2.99	**P=0.0003**	0%	5	1458	moderate

a. Subgroup analysis based on the four *a priori* groups of varied duration and dosage were not significantly different from each other.
b. Sensitivity analysis did not identify a significant effect estimate
c. Improved with sensitivity analysis

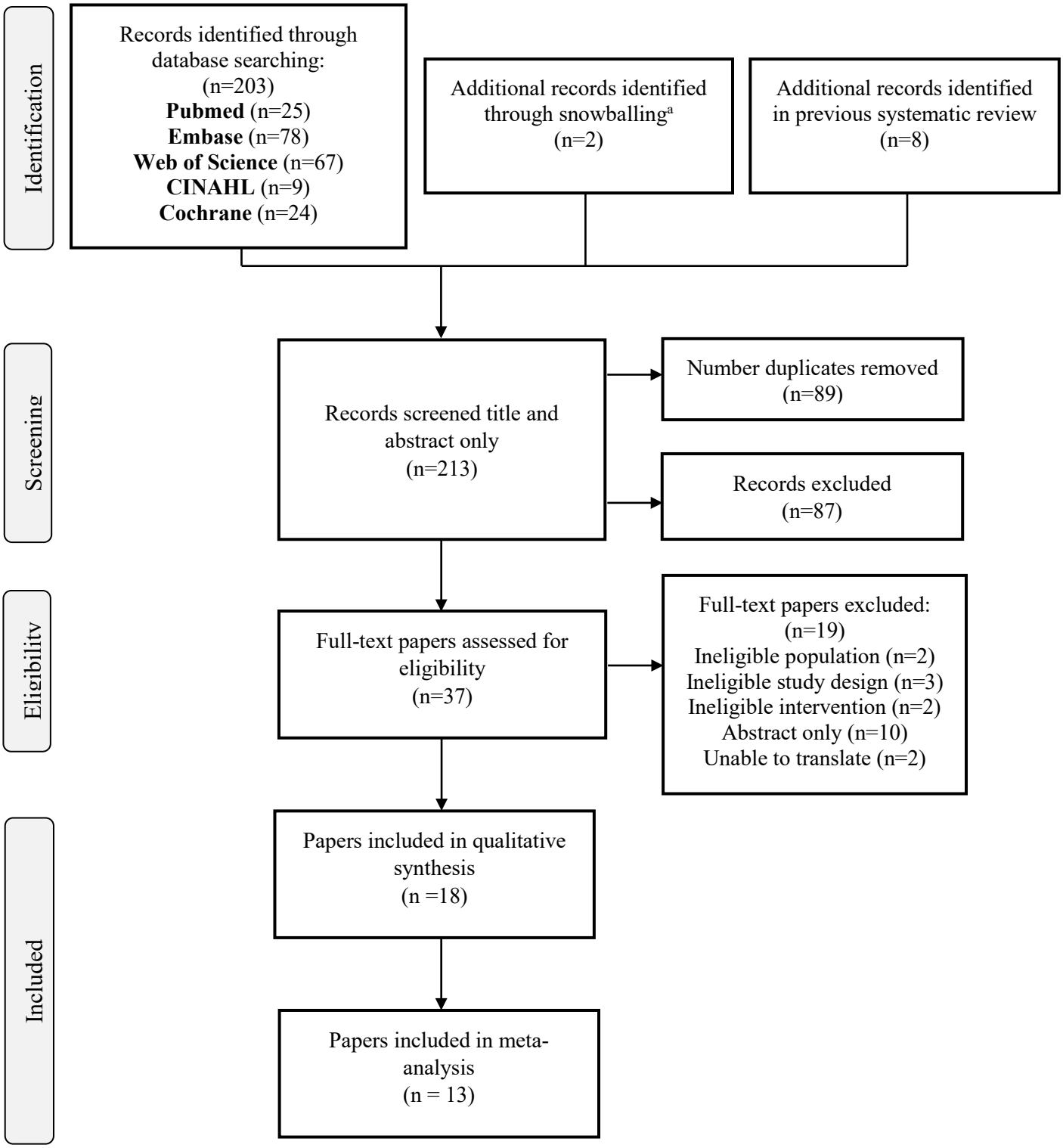

Figure 1. PRISMA flowchart of the search results and included papers in this systematic review with meta-analyses aiming to evaluate, in adult cancer patients receiving chemotherapy, the effects of ginger supplementation dose and duration on the incidence and severity of chemotherapy-induced nausea and vomiting and outcomes related to chemotherapy-induced nausea and vomiting (quality of life, fatigue). [a] Reference lists of included studies and previous systematic and narrative reviews were examined to identify additional studies not found in the systematic search strategy.

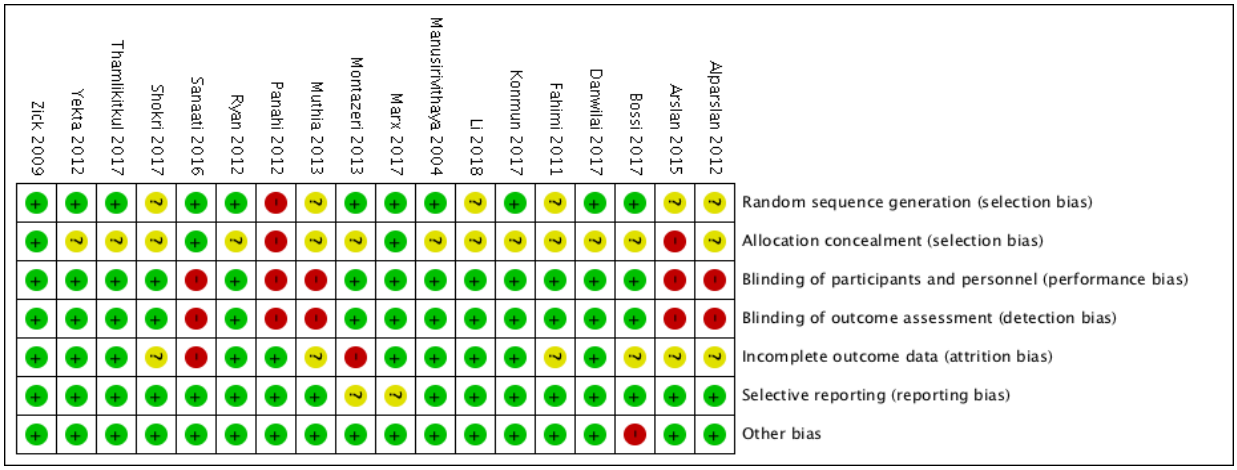

Figure 2. Risk of bias summary: Judgements from the review authors about bias in each paper included in this systematic review with meta-analyses aiming to evaluate, in adult cancer patients receiving chemotherapy, the effects of ginger supplementation dose and duration on the incidence and severity of chemotherapy-induced nausea and vomiting and outcomes related to chemotherapy-induced nausea and vomiting (quality of life, fatigue).

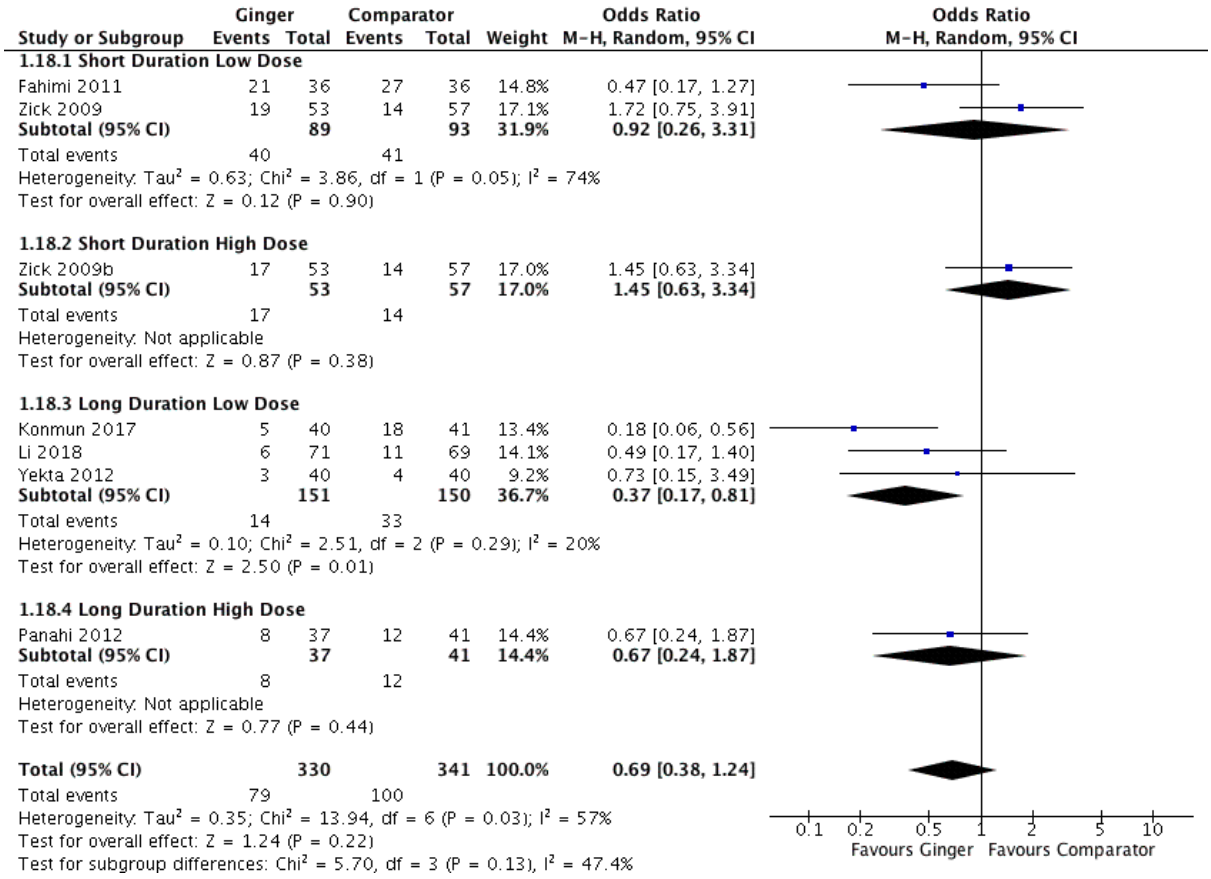

Figure 3. The likelihood of acute vomiting was reduced in adults undergoing chemotherapy by 60% with ginger supplementation of ≤1g/day for >3-days compared to control groups (OR: 0.4, 95% CI: 0.17-0.81; P=0.01; n=3 studies; n=3 interventions; n=301 participants; I^2=20%; GRADE level: moderate). Short Duration=≤3-days. Long Duration=>3-days. Low Dose=≤1g/day. High dose=>1g/day. OR=Odds ratio. CI=Confidence Interval.

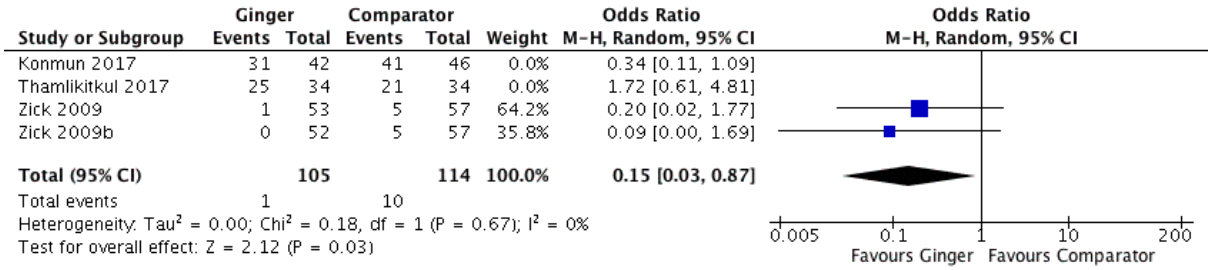

Figure 4. The likelihood of fatigue was reduced by 80% with ginger supplementation of any dose for <3-days duration compared to control groups (OR: 0.2, 95% CI: 0.03-0.87; P=0.03; n=1 studies; n=2 interventions; n=219 participants; I^2=0%; GRADE level: low). Sensitivity analysis: studies which administered intervention for >3 days were excluded. OR=Odds ratio. CI=Confidence Interval.

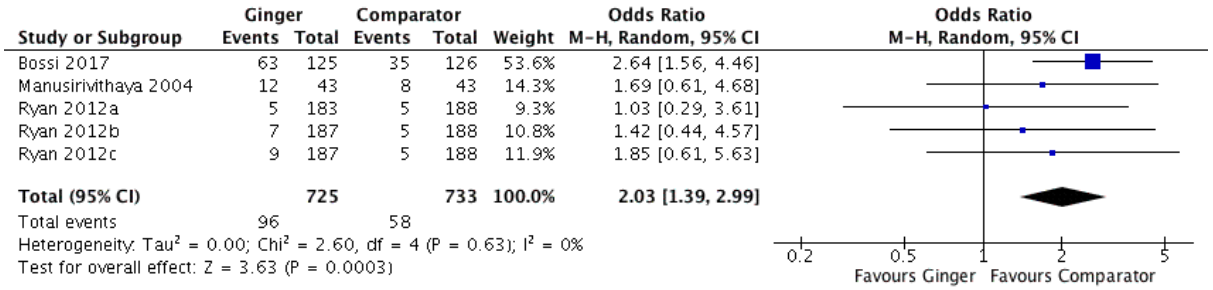

Figure 5. The likelihood of any gastrointestinal, flushing, rash-related or unspecified adverse event reasonably relatable to the intervention was increased in adults undergoing chemotherapy with ginger supplementation of any dose for any duration (OR: 2.0, 95% CI: 1.39-2.99; P=0.0003; n=3 studies; n=5 interventions; 1458 participants; I^2=0%; GRADE level: moderate). OR=Odds ratio. CI=Confidence Interval.

Online Supplementary Material 1: Database Search Strategies

Pubmed Database:

(ginger[MeSH] OR ginger*[tiab] OR zingiber officinale*[tiab] OR “officinales, zingiber”[tiab]) AND (neoplasms[MeSH] OR “chemotherapy, adjuvant”[MeSH] OR “consolidation chemotherapy”[MeSH] OR “induction chemotherapy”[MeSH] OR “photochemotherapy”[MeSH] OR “maintenance chemotherapy”[MeSH] OR “chemotherapy, cancer, regional perfusion”[MeSH] OR “antineoplastic combined chemotherapy protocols”[MeSH] OR “electrochemotherapy”[MeSH] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignanc*[tiab] OR cancer*[tiab] OR chemotherap*[tiab] OR “antineoplastic combined chemotherapy regimens” [tiab] OR antineoplastic chemotherapy protocol*[tiab] OR “chemotherapy protocol, antineoplastic” [tiab] OR “protocol, antineoplastic chemotherapy” [tiab] OR cancer chemotherapy protocol*[tiab] OR “protocol, cancer chemotherapy” [tiab] OR “adjuvant chemotherapy” [tiab] OR “consolidation chemotherapies” [tiab] OR “chemotherapy, consolidation” [tiab] OR “regional perfusion antineoplastic chemotherapy” [tiab] OR “isolation perfusion cancer chemotherapy” [tiab] OR “cancer chemotherapy, regional perfusion” [tiab] OR “perfusion cancer chemotherapy, regional” [tiab] OR “regional perfusion cancer chemotherapy” [tiab] OR electrochemotherapies OR “chemotherapy, induction” [tiab] OR “maintenance chemotherapies”[tiab] OR photochemotherapies[tiab] AND (nausea[MeSH] OR vomiting [MeSH] OR emetics[MeSH] OR Antiemetics[MeSH] OR emesis[tiab] OR emetogenic[tiab] OR emetogenicity[tiab] OR nausea[tiab] OR nauseous[tiab] OR vomit*[tiab] OR emetic*[tiab] OR regurgit*[tiab]) OR “chemotherapy induced nausea and vomiting” [tiab] OR “chemotherapy-induced nausea and vomiting” [tiab] OR CINV[tiab] AND (Randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical study[pt] OR clinical trial[pt] OR comparative study[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR “Single blind”[tiab] OR “Double blind”[tiab] OR intervention[tiab])

Web of Science Database:

((ginger OR ginger* OR "zingiber officinale*" OR "officinales, zingiber") AND (neoplasms OR "chemotherapy, adjuvant" OR "consolidation chemotherapy" OR "induction chemotherapy" OR photochemotherapy OR "maintenance chemotherapy" OR "chemotherapy, cancer, regional perfusion" OR "antineoplastic combined chemotherapy protocols" OR electrochemotherapy OR neoplas* OR tumor* OR tumour* OR malignanc* OR cancer* OR chemotherap* OR "antineoplastic combined chemotherapy regimens" OR "antineoplastic chemotherapy protocol*" OR "chemotherapy protocol, antineoplastic" OR "protocol, antineoplastic chemotherapy" OR "cancer chemotherapy protocol*" OR "protocol, cancer chemotherapy" OR "adjuvant chemotherapy" OR "consolidation chemotherapies" OR "chemotherapy, consolidation" OR "regional perfusion antineoplastic chemotherapy" OR "isolation perfusion cancer chemotherapy" OR "cancer chemotherapy, regional perfusion" OR "perfusion cancer chemotherapy, regional" OR "regional perfusion cancer chemotherapy" OR electrochemotherapies OR "chemotherapy, induction" OR "maintenance chemotherapies" OR photochemotherapies OR "chemotherapy induced nausea and vomiting" OR "chemotherapy-induced nausea and vomiting" OR CINV) AND (nausea OR vomiting OR emetics OR Antiemetics OR emesis OR emetogenic OR emetogenicity OR nausea OR nauseous OR vomit* OR

emetic* OR regurgit*) AND ("Randomized controlled trial" OR "controlled clinical trial" OR "clinical study" OR "clinical trial" OR "comparative study" OR randomized OR randomised OR placebo OR randomly OR trial OR groups OR "Single blind" OR "Double blind" OR intervention))

Embase Database:

('ginger'/exp OR ginger*:ti,ab OR 'zingiber officinale*':ti,ab OR 'officinales, zingiber':ti,ab) AND ('neoplasms'/exp OR 'chemotherapy, adjuvant'/exp OR 'consolidation chemotherapy'/exp OR 'induction chemotherapy'/exp OR 'photochemotherapy'/exp OR 'maintenance chemotherapy'/exp OR 'chemotherapy, cancer, regional perfusion'/exp OR 'antineoplastic combined chemotherapy protocols'/exp OR 'electrochemotherapy'/exp OR neoplas*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR malignanc*:ti,ab OR cancer*:ti,ab OR chemotherap*:ti,ab OR 'antineoplastic combined chemotherapy regimens':ti,ab OR 'antineoplastic chemotherapy protocol*':ti,ab OR 'chemotherapy protocol, antineoplastic':ti,ab OR 'protocol, antineoplastic chemotherapy':ti,ab OR 'cancer chemotherapy protocol*':ti,ab OR 'protocol, cancer chemotherapy':ti,ab OR 'adjuvant chemotherapy':ti,ab OR 'consolidation chemotherapies':ti,ab OR 'chemotherapy, consolidation':ti,ab OR 'regional perfusion antineoplastic chemotherapy':ti,ab OR 'isolation perfusion cancer chemotherapy':ti,ab OR 'cancer chemotherapy, regional perfusion':ti,ab OR 'perfusion cancer chemotherapy, regional':ti,ab OR 'regional perfusion cancer chemotherapy':ti,ab OR electrochemotherapies OR 'chemotherapy, induction':ti,ab OR 'maintenance chemotherapies':ti,ab OR photochemotherapies:ti,ab OR 'chemotherapy induced nausea and vomiting':ti,ab OR 'chemotherapy-induced nausea and vomiting':ti,ab OR cinv:ti,ab) AND ('nausea'/exp OR 'vomiting'/exp OR 'emetics'/exp OR 'antiemetics'/exp OR emesis:ti,ab OR emetogenic:ti,ab OR emetogenicity:ti,ab OR nausea:ti,ab OR nauseous:ti,ab OR vomit*:ti,ab OR emetic*:ti,ab OR regurgit*:ti,ab) AND ('randomized controlled trial':it OR 'controlled clinical trial':it OR 'clinical study':it OR 'clinical trial':it OR 'comparative study':it OR randomized:ti,ab OR randomised:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab OR 'single blind':ti,ab OR 'double blind':ti,ab OR intervention:ti,ab)

CINAHL Database:

((((MH "ginger+") OR TI ginger* OR AB ginger* OR TI "zingiber officinale*" OR AB "zingiber officinale*" OR TI "officinales, zingiber" OR AB "officinales, zingiber") AND ((MH "neoplasms+") OR (MH "chemotherapy, adjuvant+") OR (MH "consolidation chemotherapy+") OR (MH "induction chemotherapy+") OR (MH "photochemotherapy+") OR (MH "maintenance chemotherapy+") OR (MH "chemotherapy, cancer, regional perfusion+") OR (MH "antineoplastic combined chemotherapy protocols+") OR (MH "electrochemotherapy+") OR TI neoplas* OR AB neoplas* OR TI tumor* OR AB tumor* OR TI tumour* OR AB tumour* OR TI malignanc* OR AB malignanc* OR TI cancer* OR AB cancer* OR TI chemotherap* OR AB chemotherap* OR TI "antineoplastic combined chemotherapy regimens" OR AB "antineoplastic combined chemotherapy regimens" OR TI "antineoplastic chemotherapy protocol*" OR AB "antineoplastic chemotherapy protocol*" OR TI "chemotherapy protocol,

antineoplastic" OR AB "chemotherapy protocol, antineoplastic" OR TI "protocol, antineoplastic chemotherapy" OR AB "protocol, antineoplastic chemotherapy" OR TI "cancer chemotherapy protocol*" OR AB "cancer chemotherapy protocol*" OR TI "protocol, cancer chemotherapy" OR AB "protocol, cancer chemotherapy" OR TI "adjuvant chemotherapy" OR AB "adjuvant chemotherapy" OR TI "consolidation chemotherapies" OR AB "consolidation chemotherapies" OR TI "chemotherapy, consolidation" OR AB "chemotherapy, consolidation" OR TI "regional perfusion antineoplastic chemotherapy" OR AB "regional perfusion antineoplastic chemotherapy" OR TI "isolation perfusion cancer chemotherapy" OR AB "isolation perfusion cancer chemotherapy" OR TI "cancer chemotherapy, regional perfusion" OR AB "cancer chemotherapy, regional perfusion" OR TI "perfusion cancer chemotherapy, regional" OR AB "perfusion cancer chemotherapy, regional" OR TI "regional perfusion cancer chemotherapy" OR AB "regional perfusion cancer chemotherapy" OR electrochemotherapies OR TI "chemotherapy, induction" OR AB "chemotherapy, induction" OR TI "maintenance chemotherapies" OR AB "maintenance chemotherapies" OR TI photochemotherapies OR AB photochemotherapies OR TI "chemotherapy induced nausea and vomiting" OR AB "chemotherapy induced nausea and vomiting" OR TI "chemotherapy-induced nausea and vomiting" OR AB "chemotherapy-induced nausea and vomiting" OR TI CINV OR AB CINV AND ((MH "nausea+") OR (MH "vomiting+") OR (MH "emetics+") OR (MH "Antiemetics+") OR TI emesis OR AB emesis OR TI emetogenic OR AB emetogenic OR TI emetogenicity OR AB emetogenicity OR TI nausea OR AB nausea OR TI nauseous OR AB nauseous OR TI vomit* OR AB vomit* OR TI emetic* OR AB emetic* OR TI regurgit* OR AB regurgit*)))

Cochrane Library Database:

#1 MeSH descriptor: [Ginger] explode all trees

#2 MeSH descriptor: [Neoplasms] explode all trees

#3 (ginger*:ti,ab or "zingiber officinale*":ti,ab or "officinales, zingiber":ti,ab)

#4 #1 or #3

#5 (neoplas*:ti,ab or tumor*:ti,ab or tumour*:ti,ab or malignanc*:ti,ab or cancer*:ti,ab or chemotherap*:ti,ab or "antineoplastic combined chemotherapy regimens":ti,ab or "antineoplastic chemotherapy protocol*":ti,ab or "chemotherapy protocol, antineoplastic":ti,ab or "protocol, antineoplastic chemotherapy":ti,ab or "cancer chemotherapy protocol*":ti,ab or "protocol, cancer chemotherapy":ti,ab or "adjuvant chemotherapy":ti,ab or "consolidation chemotherapies":ti,ab or "chemotherapy, consolidation":ti,ab or "regional perfusion antineoplastic chemotherapy":ti,ab or "isolation perfusion cancer chemotherapy":ti,ab or "cancer chemotherapy, regional perfusion":ti,ab or "perfusion cancer chemotherapy, regional":ti,ab or "regional perfusion cancer chemotherapy":ti,ab or electrochemotherapies or "chemotherapy, induction":ti,ab or "maintenance chemotherapies":ti,ab or photochemotherapies:ti,ab or "chemotherapy

induced nausea and vomiting":ti,ab or "chemotherapy-induced nausea and vomiting":ti,ab or CINV:ti,ab)

#6 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees

#7 MeSH descriptor: [Consolidation Chemotherapy] explode all trees

#8 MeSH descriptor: [Induction Chemotherapy] explode all trees

#9 MeSH descriptor: [Photochemotherapy] explode all trees

#10 MeSH descriptor: [Maintenance Chemotherapy] explode all trees

#11 MeSH descriptor: [Chemotherapy, Cancer, Regional Perfusion] explode all trees

#12 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees

#13 MeSH descriptor: [Electrochemotherapy] explode all trees

#14 #2 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 MeSH descriptor: [Nausea] explode all trees

#16 MeSH descriptor: [Vomiting] explode all trees

#17 MeSH descriptor: [Emetics] explode all trees

#18 MeSH descriptor: [Antiemetics] explode all trees

#19 (emesis:ti,ab or emetogenic:ti,ab or emetogenicity:ti,ab or nausea:ti,ab or nauseous:ti,ab or vomit*:ti,ab or emetic*:ti,ab or regurgit*:ti,ab)

#20 #15 or #16 or #17 or #18 or #19

#21 ("Randomized controlled trial":pt or "controlled clinical trial":pt or "clinical study":pt or "clinical trial":pt or "comparative study":pt or randomized:ti,ab or randomised:ti,ab or placebo:ti,ab or randomly:ti,ab or trial:ti,ab or groups:ti,ab or "Single blind":ti,ab or "Double blind":ti,ab or intervention:ti,ab)

#22 #4 and #14 and #20 and #21

Online Supplementary Material 2: Cochrane Risk of Bias Assessment

Table 1. Cochrane Risk of Bias assessment with justifications for included studies located in the updated search (n=13), examining the effect of ginger supplementation on chemotherapy-induced nausea and vomiting incidence and related outcomes.

	Study	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**	**Other bias**
Rating	Alparslan 2012	Risk of bias: Unclear	Risk of bias: Unclear	Risk of bias: High	Risk of bias: High	Risk of bias: Unclear	Low	Low
Evidence		No mention of description of randomisation or how participants were allocated to each group. However, no difference between baseline characteristics (P>0.05).	No description of how allocation was conducted.	No attempt at blinding made (Intervention group received ginger tablet and no anti-emetics, control group received anti-emetics and no ginger) therefore outcomes likely to be influenced (more so nausea than vomiting incidence) and effect of intervention may have been overestimated.	Vomiting incidence objective, however, nausea subjective and assessment completed by participants who were not blinded to the intervention or outcome, therefore likely to effect outcome and effect of intervention may have been overestimated.	No raw data provided (tables missing from paper) therefore no indication of attrition.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Arslan 2015	Risk of bias: High	Risk of bias: High	Risk of bias: High	Risk of bias: High	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low
Evidence		"No significant differences were seen between the intervention and control group (p>0.05)" however, the raw data was not reported and the patients were "randomized sequentially to the two groups (control and intervention); that is, the first patient was assigned to the control group and the next one to the intervention group." I.e. alternate allocation / quasi-randomisation used	The patients were randomised sequentially to the two groups (control and intervention); that is, the first patient was assigned to the control group and the next one to the intervention group, therefore allocation concealment inadequate.	No attempt at blinding made (Intervention group received ginger powder, control group received nothing) therefore outcomes likely to be influenced (more so nausea than vomiting incidence) and effect of intervention may have been overestimated.	"The patient diary was given to the patients in the intervention and control groups, and they were asked to complete the diary four times a day at home". Vomitting incidence objective, however, nausea subjective and assessment completed by participants who were not blinded to the intervention, therefore likely to effect outcome and effect of intervention may have been overestimated.	No mention of attrition or sample size per group.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.

		which is predictable and likely to create differences between the groups.						
Rating	Bossi 2017	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: High
Evidence		"patients were randomly assigned, according to a pre-defined computer generated list (RALLOC of STATA)." Baseline characteristics not statistically analysed, however appear similar suggesting randomisation executed successfully.	No description of how allocation was conducted.	"double-blind, placebo-controlled trial". Either ginger extract 40mg/capsule (provided by Helsinn) or matching placebo.	"All patients received a patient diary" with questionnaires. As patients blinded to outcomes, unlikely to have influenced results.	"39% participants withdrew prematurely" however "dropout rate did not differ between treatment groups (ginger: 42.4%; placebo 34.9%; P=0.22)." Intention to treat used but n=251 before attrition, n=244 included in results.	Study protocol identified and all pre-specified expected outcomes included in publication as intended.	Some authors are paid or employed by funding company.
Rating	Danwilai 2017	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		"participants were randomly assigned into two groups using a block of four randomization techniques. The study coordinator generated a randomization list to assign participants to receive either ginger extract (stan- dardized 6-gingerol) or placebo." Randomisation thought to be successfully executed given that there was "no difference	No description of how allocation was conducted.	"double-blind, placebo controlled trial". "The standardized 6-gingerol and placebo capsules were placed into packages of similar color and size."	"The investigators and participants were blinded to the randomization list and treatment assignments."	14% attrition. 6 withdrawn from ginger group, one from placebo, however, no statistical analysis done between groups however likely to be insignificant and not effect results.	None detected	The study appears to be free of other sources of bias.

		between baseline characteristics (P>0.05)."						
Rating	Konmun 2017	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		Particpants were "randomly assigned... utilizing a block four method for randomization." Randomisation thought to be successfully executed given that there were no differences between baseline characteristics reported.	No description of how allocation was conducted.	"double-blind, placebo-controlled trial" "placebo capsules … match the weight of the 6-gingerol capsules"	"patients were required to complete a daily diary … The diary included number of vomiting episodes, nausea score, appetite score, quality of life, use of rescue anti-emetic, and hospitalization." As patients blinded to outcomes well, unlikely to have influenced results.	14% attrition. Withdrawal numbers and reasons similar between groups. Atrrition well documented.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Li 2018	Risk of bias: Unclear	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		No mention of description of randomisation or how participants were allocated to each group. However, no difference between baseline characteristics (P>0.05).	No description of how allocation was conducted.	"double-blind, placebo-controlled clini- cal trial" "The placebo capsules were physically identical to the ginger capsules"	Both participants and researchers blinded to outcomes.	4% attrition. Reasons for this and numbers per group given. No intention to treat used however, 6 drop outs unlikely to influence results.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Marx 2017	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low

Evidence		"randomly allocated… by an independent company using a computer-generated sequence." Baseline characteristics not statistically analysed, however appear similar suggesting randomisation executed successfully.	"Eligible patients were randomly allocated to ginger or placebo capsules by *an independent company* using a computer-generated sequence."	"All staff members involved in recruitment and outcome assessment were blinded to the results of randomization." Placebo capsules same appearance and weight. Double-enapsulated.	Participants self-completed questionnaires and blinded to outcomes.	Intention to treat used (34/51 completed all cycles, however, 51 included in analysis). Attrition well documented.	Results reported differ from those pre-specified in study protocol, however, explanations provided in publication.	The study appears to be free of other sources of bias.
Rating	Montazeri 2013	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: High	Risk of bias: Unclear	Risk of bias: Low
Evidence		"This study is a randomized, prospective, cross-over double - blinded clinical trial," "This study was doing on the basis of the block randomization with the four block method."	No description of how allocation was conducted.	"Double-blind, placebo-controlled trial" "The shape, colour and fragrance of this powder were similar to ginger and both of them were provided by the same company."	Both participants and researchers blinded to outcomes.	32% attrition. 13/44 unable to complete second cycle of study. Reasons for this given but dropouts per group not given. Unclear whether intention to treat used.	Unclear whether outcome data missing from analysis and whether this could have effect on results.	The study appears to be free of other sources of bias.
Rating	Muthia 2013	Risk of bias: Unclear	Risk of bias: Unclear	Risk of bias: High	Risk of bias: High	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low
Evidence		No mention or description of randomisation or how participants were allocated to each group. No statistical analysis of baseline characteristics to determine whether sequence generation free from bias.	No description of how allocation was conducted.	No attempt at blinding made (Intervention group received ginger drink, control group did not) therefore outcome of vomiting and mainly nausea likely to be influenced and effect of intervention may have been overestimated.	Rhodes Index for Nausea, Vomiting and Retching subjective and seeing as participants and researchers not blinded to treatment and outcomes, likely to influence results and effect of intervention may have been overestimated.	No mention of attrition or sample size per group.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Sanaati 2016	Risk of bias: Low	Risk of bias: Low	Risk of bias: High	Risk of bias: High	Risk of bias: High	Risk of bias: Low	Risk of bias: Low

Evidence		"randomly allocated …using the 20 block random tables." Randomisation thought to be successfully executed given that there was no difference between baseline characteristics reported (P>0.05).	Coding and blinding of the two groups were performed privately by the pharmacologist consultant.	Control group given no intervention, treatment groups aware receiving intervention and only blinded to whether receiving ginger or chamomile capsules. Outcome likely to be influenced and effect of intervention may have been overestimated.	"A self-made, two-part self- reporting instrument was used to measure the frequency and severity of nausea and vomiting". Frequency of vomitting objective, however, nausea frequency/severity and vomitting severity subjective outcomes likely to be influenced by the fact that participants were not blinded to receiving treatment/not and effect of intervention may have been overestimated.	30% attrition. 13 out of 43 interrupted their participation (excluding chamomile group). Reasons given, however, no differentiation between groups and number of drop outs per group not given. No intention to treat used.	Study Protocol pre-registered and all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Shokri 2017	Risk of bias: Unclear	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low
Evidence		"The patients were divided into 2 random groups. They were then divided into 2 homogeneous groups (using Randlist) based on their satisfaction to receive ginger in terms of the history of lack of neoplastic diseases in women, history of lack of chemotherapy and stage of cancer." Unclear whether those that were happy to receive and comply with ginger intervention more likely to be allocated that intervention. However, no statistically signficant differences between other baseline characteristcs .	No description of how allocation was conducted.	"Examiners and the patients were unaware of the coding and the real grouping was only specified after statistical analysis." Placebo used.	No indication how nausea and vomitting outcome assessed. As participants and researchers blinded to intervention, unlikely to effect outcomes.	No mention of attrition or sample size per group.	Study Protocol pre-registered and all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Thamlikitkul 2017	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low

Evidence		"subjects were randomly assigned in a 1:1 ratio from the stratified randomization table." Baseline characteristics not reported per group due to cross over design.	No description of how allocation was conducted.	"The placebo and ginger capsules and their packaging were physically identical. The investigators and subjects were blinded to the randomization list and treatment assignments."	Participants filled out questionnaires and were blinded to outcome measures and intervention, therefore unlikely to effect outcomes.	No attrition, all participants completed the study.	Study Protocol pre-registered and all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Yekta 2012	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		"The patients were randomly allocated…using the 20 block random tables." No statistically signficant differences between baseline characteristcs suggesting randomisation executed successfully.	No description of how allocation was conducted.	"placebo capsules ... exactly the same size, shape, color, taste, and dosage as Zintoma capsules." "Coding and blinding of the 2 groups were performed privately by the pharmacologist consultant, and all of the samples, data analyzers, and all participants too, were unaware of the real content of the capsule"	Participants used self-reporting instruments to document outcomes and seeing as participants were blinded to intervention, unlikely to have effected results. Outcome of vomiting incidence objective rather than subjective.	18% attrition relatively low, reasons given for this along with numbers per group. No intention to treat used however, 18 drop outs unlikely to influence results.	Study Protocol pre-registered and all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.

Table 2. Cochrane Risk of Bias assessment with justifications for included studies located in the researchers' previous systematic review (n=5), examining the effect of ginger supplementation on chemotherapy-induced nausea and vomiting incidence and related outcomes.

Rating	Fahimi 2011	Risk of bias: Unclear	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low
Evidence		Participants randomised, however, specific information on how this was carried out not given. Baseline characteristics not reported per group due to cross over design.	"The monitoring investigator dispensed either active drug or placebo according to the randomization table." No information given as to whether or not this was concealed.	Placebo capsules were "identical". Participants were blinded to the intervention received also.	Questionnaires given to particpant to complete, and seeing as patients blinded to intervention, unlikely to have effected results.	28% attrrition. 36/50 completed the study. Reasons given, however, did not specify which intervention they were undergoing when they discontinued therefore unsure whether relatable to the ginger intervention. Unclear whether intention to treat used.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Manusirivithaya 2004	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		Participants were "randomly assigned by block of four." Baseline characteristics not reported per group due to cross over design.	No description of how allocation was conducted.	Participants and research team blinded to intervention. "All of these capsules were identical in appearance, contour, size, and color."	Scale of nausea severity self-reported. Both participants and researchers blinded to outcomes.	10% attrition. Reasons not given, however numbers per regimen given and same for each group. Intention to treat not used (48 recruited, 43 only included in data analysis), however, not likely to effect results.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Panahi 2012	Risk of bias: High	Risk of bias: High	Risk of bias: High	Risk of bias: High	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low

Evidence		"The participants of this open-label trial were individually and alternatively allocated to ginger or control group with the first allocation being chosen randomly. At the beginning of study and before patient recruitment, blank questionnaires were numbered and alternatively coded as ginger or control. The first code was chosen randomly (by lottery)."	The patients were randomised sequentially to the two groups (control and intervention); that is, the first patient was assigned to the control group and the next one to the intervention group, therefore allocation concealment inadequate.	No placebo used therefore participants and researchers not blinded to the intervention. Therefore outcomes likely to be influenced and effect of intervention may have been overestimated.	Questionnaires were self reported. However, participants knew which intervention they received therefore likely to influence results and overestimate effect of intervention.	22% attrition (22/100 didn't complete the study). Reasons given and numbers per group and dropout rate not statistically significantly different between the groups. Intention to treat appears not to have been, however, 22 drop outs unlikely to affect results.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Ryan 2012	Risk of bias: Low	Risk of bias: Unclear	Risk of bias: Low	Risk of bias:	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		"Randomization was stratified by CCOP site. Within each site, a computer-generated random number table with block size eight was used to randomly assign patients to one of four treatment arms." No statistically signficant differences between baseline characteristcs suggesting randomisation executed successfully.	No description of how allocation was conducted.	Placebo capsules made to be identical in weight and appearance, and double encapsulated.	Questionnaires given to participant to complete, and seeing as patients blinded to intervention, unlikely to have effected results.	23% attrition. Some intention to treat used where possible. Numbers per group and reasons given.	Study Protocol pre-registered and all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.
Rating	Zick 2009	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low	Risk of bias: Low
Evidence		"The randomization code blocked by research site was computer-generated by the study biostatistician." Baseline characteristics not statistically analysed, however appear similar suggesting randomisation executed successfully.	" All study participants as well as all study personnel who assessed outcomes, worked with study data, or administered tests or questionnaires were unaware of the randomization list or treatment assignment. "	"All study participants as well as all study personnel who assessed outcomes, worked with study data, or adminis- tered tests or questionnaires were unaware of the randomization list or treatment assignment." Placebo capsules made to mimic ginger.	As participants and researchers blinded to intervention, unlikely to effect outcomes.	20% attrition (33/162). Intention to treat used. Reasons per group for drop outs given, numbers and reasons don't appear drastically different between groups.	No study protocol identified, however, all pre-specified expected outcomes included in publication as intended.	The study appears to be free of other sources of bias.

Online Supplementary Material 3: Characteristics of Included Studies

Table 1. Included studies located in the updated search strategy (n=13), examining the effect of ginger supplementation on chemotherapy-induced nausea and vomiting incidence and chemotherapy-related outcomes.

Citation	Study Design & Setting	Population	CTx Protocol	Adjuvant Therapies	Intervention Group/s (IG)	Comparator Group/s (CG)	Results
Alparslan 2012 (24)	Design: Non-RCT Country: Turkey Study Duration Dates: March 2011 to July 2011	N: 45 Attrition: 0% Females: n=15 Age: 60% were 46-80 years Cancer type: Hematological (64% leukaemia) History of CINV: Not specified	None specified. 51% were on their first course of treatment	None specified	n: 15 Type: ginger tablet Dose: 1.6g/d (2x0.4g BD) Duration: Throughout course of treatment (length unspecified)	n: 30 Type: IV anti-emetic (3mg setron)	**CINV**[a] Incidence (time point not specified): - IG n=0/15; CG n=23/30; **P<0.05** between groups **Mortality** Not reported
Arslan 2015 (25)	Design: RCT Country: Turkey Dates: Not specified	N: 60 Attrition: 0% Female: n=60 Age: mean 48.5 years Cancer: Breast cancer (stage II or III) with previous surgical treatment History of CINV: Yes, established in previous Cycles. No difference between groups	Drugs: Anthracycline, cyclophosphamide, doxorubicin and 5-fluorouracil Emetogenicity: Not specified Single or multi day: Single Commencing Cycle: ≥2nd Cycle Cycle length: Not specified	5-HT3 receptor antagonist (palonosetron), dexamethasone, an antihistamine (ranitidine((Day 1); PO aprepitant (Days 1-3)	n: 30 Type: 0.5g powdered ginger sachet mixed with yoghurt Dose: 1g/d (0.5g BD) Duration: 3 days; 1st dose 30 mins before CTx; for 2 Cycles	n: 30 Type: Standard care (no ginger)	**CIN** Severity (mean score (SD); specially formulated tool; score ranges 0-10; higher score indicates more severe CIN): - *Day 1 (acute severity):* IG 0.8 (0.9); CG 1.2 (1.1); P=0.15 between groups - *Day 2:* IG 3.8 (1.9); CG 6.3 (1.9); **P<0.001** between groups - *Day 3:* IG 3.8 (1.8); CG 6.5 (1.8); **P=0.001** between groups - *Day 4:* IG 3.7 (1.9); CG 6.3 (1.8); **P=0.001** between groups - *Day 5:* IG 2.8 (1.7); CG 5.4 (2.3); **P=0.001** between groups - *Overall Severity (mean of Day 1-5 scores):*[b] IG 2.98 (1.64); CG 5.14 (1.78) - *Delayed Severity (mean of Day 2-5 scores):*[b] IG 3.53 (1.83); CG 6.13 (1.95) - *Delayed Nausea (time point not specified):* IG 3.6 (1.8); CG 6.1 (1.7); **P<0.001** between groups - *Acute Nausea (time point not specified):* IG 1.6 (1.1); CG 3.9 (1.6); **P<0.001** between groups - *Before Intervention (time point not specified):* IG 5.3 (1.0); CG 5.2 (1.5); P=0.9 between groups - *After Intervention (time point unclear):* IG 3 (1.5); CG 5.1 (1.5); **P<0.001** between groups **CIV** Incidence (mean number of episodes (SD); measured 4 times each day): - *Day 1:* IG 0 (0.1); CG 0.1 (0.2); P=0.21 between groups - *Day 2:* IG 0 (0.1); CG 0.3 (0.6); **P=0.01** between groups - *Day 3:* IG 0 (0.1); CG 0.2 (0.4); **P=0.01** between groups - *Day 4:* IG 0 (0.1); CG 0.1 (0.4); **P=0.07** between groups - *Day 5:* IG 0 (0.0); CG 0.2 (0.4); **P=0.04** between groups - *After Intervention (time point unclear):* IG 0 (0); CG 0.2 (0.3); **P=0.011** between groups **Mortality** Not reported

Bossi 2017 (39)	Design: Double-blind placebo-controlled randomised trial Country: Italy Data Collection Dates: June 2013 to April 2015	N: 251 Attrition: n=97 (39%); IG n=53; CG n=44 Female: n=84 Age: μ59±10 years Cancer: n=119 lung, n=86 head and neck, n=21 bladder, n=18 other History of CINV: No Reasons for attrition: n=25 adverse events (IG n=13, CG n=12), n=24 withdrew consent, n=1 loss to follow-up, n=2 protocol violations, n=45 other	Drugs: Cisplatin >50mg/m^2 and other unspecified Emetogenicity: High Single or multi day: Single Commencing Cycle: Cycle 1 Cycle length: n=140 were 21 days. N=4 were 28 days	Aprepitant and 5-HT3 receptor antagonist (Day 1); dexamethasone (Days 1-4)	n: 125 Type: Softel capsule with sunflower oil (110 mg) and zingiber officinalis standardised CO2 supercritical extract (40mg); minimum Gingerols 16mg, min Shogaol 1.12mg Dose: 0.16g/d (2x0.04g BD). Duration: 42-56 days covering n=2 Cycles, commenced on Day 2 of each 21-28-day Cycle	n: 126 Type: Placebo of softgel capsule 150mg sunflower oil	**CIN** Any nausea incidence (VAS Score >5/100; OR <1.00 when IG had better protective effect against CIN that CG; measured daily): - *C1 Day 2 to 5:* IG n=77/121; CG n=71/123; OR: 1.06 (95% CI 0.60-1.85); P=0.851 - *C2 Day 2 to 5:* IG n=52/121; CG n=55/123; OR: 1.36 (95% CI 0.69-2.70); P=0.379 - *Overall and Delayed Incidence (mean of C1 and C2 Day 2-5):*[b] IG n=65/121 CG n=63/123 - *C1 Day 6 to 20 / 27 (Intercycle):* IG n=66/121; CG n=60/123; OR: 1.31 (95% CI 0.73-2.37); P=0.367 - *C2 Day 6 to 20 / 27 (Intercycle):* IG n=46/121; CG n=47/123; OR: 1.32 (95% CI 0.68-2.58); P=0.417 - *C1 Day 21 / 28 (Anticipatory):* IG n=30/121; CG n=29/123; OR: -0.93 (95% CI 0.51-1.72); P=0.823 - *C2 Day 21 / 28 (Anticipatory):* IG n=20/121; CG n=22/123; OR: -1.20 (95% CI 0.58-2.47); P=0.629 **Physical function** FLIE Score (score ranges 18-126; higher scores indicate better physical function; measured on Days 1 and 6 of Cycle 1 and 2): - No difference between groups (data not reported) **Fatigue** BFI Score (score ranges 0-10; higher scores indicate more severe fatigue; measured on Days 1 and 6 of Cycle 1 and 2): - *C1*: treatment difference favouring ginger: 0.23, 95% CI:-0.97-0.51 - *C2:* treatment difference favouring placebo: 0.09, 95% CI: –0.71-0.89 **Adverse Events:** - 198 (78.9%) experienced 1 adverse event, no difference between groups (data not reported) - *Adverse events related to study treatment:* IG n=63/125 (51.1% mild, 33.1% moderate and 13.8% severe); CG n=35/126 (51.8% mild, 30.6% moderate and 15.6% severe) **Mortality** Not reported
Danwilai 2017 (35)	Design: Pilot double-blind placebo-RCT Country: Thailand Recruitment Dates: September 2012 to July 2013	N: 50 Attrition: n=7 (14%); IG n=6; CG n=1 Female: n=43 Age: 52.4 ± 9.1 years Cancer: Breast (91%), ovarian and lung History of CINV: No Reasons for attrition: n=3 withdrew consent, n=1 unable to swallow capsule, n=3 transferred to different site	Drugs: Mostly anthracycline based regimen or some platinum based regimen. Emetogenicity: Moderate or high Single or multi day: Not specified Commencing Cycle: Cycle 1 Cycle length: Not specified	Dexamethasone and ondansetron prior to CTx administration. Rescue anti-emetics at any time if needed. Those given aprepitants not eligible for inclusion	n: 25 Type: Capsule with 0.005g standardised 6-gingerol (1.4% w/w of ginger extract); binder; thickening agent Dose: 0.02g/d (2x 0.005g BD). Duration: from 3 days prior to CTx through to the 4th Cycle	n: 25 Type: placebo capsule with binder, thickening agent and matched weight	**Adverse Events:** - *Withdrawals:* IG 6; CG 1 - *Toxicity (n withdrawn due to unacceptable toxicity):* IG n=0/25; CG not specified - *Adverse events reasonably related to study treatment:* IG n=0/19; CG not specified **Mortality** Not reported

Konmun 2017 (36)	Design: Double-blind placebo-controlled randomised trial Country: Thailand Recruitment Dates: January 2012 to July 2013	N: 88 (n=94 randomised but n-88 commenced study) Attrition: 7 (8%) Female: n=75 Age: median 53 (range 19-81) years Cancer: Solid tumors; breast cancer (72%); with prior surgical removal History of CINV: No Reasons for attrition: n=1 protocol violation, n=6 withdrew consent	Drugs: 68% anthracycline-based, 21% platinum-based. Emetogenicity: Moderate or high Single or multi day: Not specified Commencing Cycle: Cycle 1 Cycle length: Not specified	Ondansetron and dexamethasone prior to CTx (IV Day 1, PO Days 1-4); PO Metoclopramide (days 2-4). Those given aprepitants not eligible for inclusion	n: 46 Type: Capsule with 0.005g standardised 6-gingerol (1.4% w/w of ginger extract) Dose: 0.02g/d (2x0.005g BD) Duration: from 3 days prior to CTx for at least 3 Cycles (through to 12 weeks of treatment or completion of planned CTx)	n: 42 Type: Placebo - capsules with diluents/binder and thickening agent	**CIN** Incidence (time points unclear): - *All grade combined nausea:* IG n=30/40; CG n=37/41; P=0.084 - *All grade acute nausea:* IG n=18/40; CG n=30/41; **P=0.010** - *All grade delayed nausea:* IG n=30/40; CG n=37/41; P=0.084 Severity (NRS ESAS Score; score ranges 0-10; higher scores indicate more severe CIN; measured daily 0-120hr post CTx): - *Mild nausea:* IG 55%; CG 17%; **P<0.001** - *Moderate nausea*: IG 15%; CG 39%; **P<0.001** - *Severe nausea:* IG 5%; CG 34%; **P<0.001** **CIV** Incidence (measured daily): - *All grade combined vomiting:* IG n=9/40; CG n=28/41; **P<0.001** - *All grade acute vomiting:* IG n=5/40; CG n=18/41; **P=0.002** - *All grade delayed vomiting:* IG n=9/40; CG n=28/41; **P=0.002** **Fatigue** Incidence of all grades: - IG n=31/42; CG n=41/46; **P=0.020** between groups **QoL** FACT-G Score (mean (SD); score ranges 0-108; higher score indicates better QoL; measured at end of study, Day 64 post CTx): - *Total Score:* IG 86.21 (13.6); CG 72.36 (18.9); **P<0.001** **Adverse Events** Incidence of events reasonably related to intervention: - *Toxicity:* IG n=0/42; CG n=0/46 - *Other:* IG n=0/42; CG not specified **Mortality** Not reported
Li 2018 (40)	Design: Double-blind placebo-RCT Country: China Recruitment Dates: June 2016 to March 2017	N: 146 Attrition: n=6 (4%) (IG n=2, IG n=4) Female: n=40 Age: IG 57 ± 7-8 years Cancer: lung History of CINV: IG 59%, CG 66% Reasons for attrition: self-reported lack of compliance n=6	Drugs: Cisplatin 68%, carboplatin 26%, oxaliplatin 6% Emetogenicity: Single or multi day: not specified Commencing Cycle: any Cycle length: any	Standard antiemetic therapy ($5HT_3$ RA's). 66% had aprepitants	n: 71 Type: 0.25g capsule with standardised dry ginger root powder with 0.013g (5%) gingerols Dose: 0.5g/d (2x0.25g BD) Duration: for 5 days starting on first day of CTx	n: 69 Type: 0.25g placebo capsule with corn starch	**CIN** Incidence (measured on Day 2 and 5 post CTx): - *Acute:* IG n=49/71; CG n=39/69; P=0.174 - *Delayed:* IG n=43/71; CG n=50/69; P=0.214 - *Overall Incidence (mean of acute and delayed):*[b] IG 46/71; CG 45/69 Severity Score (median MAT score (interquartile range); measured on Day 2 and 5 post CTx): - *Acute:* IG 3 (0, 4); CG 3 (0, 4); P=0.246 - *Delayed:* IG 1 (0, 5); CG 2 (0, 4.5); P=0.347 **CIV** Incidence (measured on Day 2 and 5 post CTx): - *Acute:* IG n=6/71; CG n=11/69; P=0.309 - *Delayed:* IG n=16/71; CG n=18/69; P=0.813 - *Overall Incidence (mean of acute and delayed):*[b] IG 11/71; CG 15/69 Frequency (median MAT score (interquartile range); measured on Day 2 and 5 post CTx): - *Acute:* IG 0 (0, 0); CG 0 (0, 0); P=0.256 - *Delayed:* IG 0 (0, 1); CG 0 (0, 0); P=0.718 **QoL** FACT-G Score (mean (SD); score ranges 0-108; higher score indicates better QoL; measured on Day 1 and 5 post CTx): - *Day 1:* IG 72.65 (14.00); CG 71.78 (14.68); P=0.720 - *Day 5:* IG 72.79 (14.00); CG 72.45 (13.93); P=0.884 **Adverse Events** Incidence of events reasonable related to intervention (measured anytime during study duration): - *Drowsiness:* IG n=30/71; CG n=21/69; P=0.163 - *Dry mouth:* IG n=18/71; CG n=9/69; P=0.086

							- *Heartburn:* IG n=6/71; CG n=3/69; P=0.494 - *Flushing:* IG n=11/71; CG n=5/69; P=0.184 **Mortality** Not reported
Marx 2017 (41)	Design: Double-blind placebo-RCT Country: Australia Recruitment Dates: March 2014 to February 2015	N: 51 Attrition: n=17 (33%); n=9 IG; n=8 CG Female: n=32 Age: 58 ± 12 years Cancer: 37% colon, 26%, breast, 22% lymphoma, other. History of CINV: No Reasons for attrition: n=4 adverse event (n=3 CG, n=1 IG), n=3 nausea/vomiting, n=1 loss to follow-up, n=9 withdrew consent	Drugs: Not specified Emetogenicity: 85% moderate, 16% high Single or multi day: Single day[c] Commencing Cycle: Cycle 1 Cycle length: Not specified	Standard anti-emetics prescribed by physician not specified	n: 24 Type: 0.3g capsule standardised ginger extract with 5% (0.015g) gingerols Dose: 1.2g (0.3g QID) Duration: 5 days starting on the day of CTx from Cycle 1-3	n: 27 Type: 0.3g placebo capsule with inert filler	**CIN** INVR Score (median (IQR); score ranges 0-10; higher score indicates more severe CIN): - *Acute (measured on the day of CTx) C1:* IG 3.6 (3, 5); CG 3 (3, 5); P=0.46 - *Acute C2:* IG 3 (3, 3); CG 3 (3, 4); P=0.63 - *Acute C3:* IG 3 (3, 5); CG 3 (3, 5); P=0.79 - *Delayed (combination of scores measured from Day 1 post CTx to Day 5 post CTx) C1:* IG 11 (9, 17); CG 15 (9, 20); P=0.27 - *Delayed C2:* IG 14.5 (9, 15); CG 12 (9, 16); P=0.54 - *Delayed C3*: IG 12 (9, 16.5); CG 12 (9, 16); P=0.42 **CIV** INVR Score (median (IQR)): - *Acute (measured on the day of CTx) C1:* IG 3 (3, 3); CG 3 (3, 3); P=0.41 - *Acute C2:* IG 3 (3, 3); CG 3 (3, 3); P=0.99 - *Acute C3:* IG 3 (3, 3); CG 3 (3, 3); P=0.17 - *Delayed (combination of scores measured from Day 1 post CTx to Day 5 post CTx) C1:* IG 9 (9, 9.7); CG 9 (9, 12); P=0.74 - *Delayed C2:* IG 9 (9, 10); CG 9 (9, 10); P=0.95 - *Delayed C3*: IG 9 (9, 9); CG 9 (9, 10); P=0.69 **CINV** INVR Score (median (IQR); score ranges 0-10; higher score indicates more severe CINV): - *Anticipatory (measured on the day before CTx) C1:* IG 8 (8, 8); CG 8 (8, 8); P=0.44 - *Anticipatory C2:* IG 8 (8, 9); CG 8 (8, 9); P=0.61 - *Anticipatory C3:* IG 8 (8, 8); CG 8 (8, 9); P=0.76 **QoL** CINV QoL (FLIE-5DR score; median (IQR); score ranges 18-126; higher scores indicate better QoL; measured at baseline and 4 days post CTx): - *C1:* IG 124.5 (113.2, 126); CG 111 (99, 126); **P=0.043** between groups - *C2:* IG 124 (108, 126); CG 117 (109, 126); P=0.916 between groups - *C3:* IG 123.5 (107, 126); CG 120 (111, 126); P=0.931 between groups Global Cancer-related QoL (FACT-G score; mean (SD); score ranges 0-108); higher scores indicate better QoL; measured at baseline and 4 days post CTx): - *C1:* IG 85.1 (18.9); CG 71.9 (18.3); **P=0.015** between groups - *C2:* IG 74.9 (17.7); CG 67.6 (10.2); P=0.077 between groups - *C3:* IG 83.6 (15.0); CG 75.1 (13.9); **P=0.040** between groups - Overall (mean of C1 and C3)[b]: IG 81.2 (17.2); CG 71.6 (14.1) **Fatigue** FACIT-F score (mean (SD); score ranges 0-52, higher scores indicate less fatigue; measured at baseline and 4 days post CTx): - *C1:* IG 41.8 (13); CG 32.2 (10.8); **P=0.006** between groups - *C2:* IG 37.7 (10.8); CG 34.5 (7.9); P=0.23 between groups - *C3:* IG 42.4 (10.2); CG 36.1 (7.2); **P=0.013** between groups **Adverse Events** Incidence (measured 5-days post CTx): *Overall adverse events not reasonable attributable to intervention*: IG n=1/24; CG n=3/27 *Side effects reasonably related to study treatment*: IG n=2/24 constipation, IG n=4/24 reflux, CG not specified **Mortality** Not reported

Montazeri 2013 (30)	Design: Cross-over double blinded, placebo RCT Country: Unclear, possibly Iran Data Collection Dates: September 2006 to March 2007	N: 44 Attrition: n=13 (30%) during second intervention period, unclear from which groups. Female: n=18 Age: mean 50.3 ± 3.1 years Cancer: mainly oesophagus History of CINV: Yes Reason for attrition: n=3 death, n=7 protocol violation, n=2 vomiting, n=1 loss to follow-up	Drugs: Cisplatin with or without other unspecified CTx agents (most commonly fluorouracil 5) Emetogenicity: Not specified Single or multi day: Not specified Commencing Cycle: After Cycle >1, not specified	Grainestrone and dexamthasone and metoclopramide if requested	n: Unclear; possibly 37 Type: 0.25g ginger powder capsule Dose: 1g/d (2x 0.25g BD) Duration: for one Cycle (at least 28 days) before crossing over	n: Unclear; possibly 37 Type: 0.25g placebo capsule with chickpea flour (2x 0.25g BD)	**CINV** Severity (Strain Tools of Severity; score ranges 0-10; higher score indicates more severe CIN; measured 7,8,9,10 and 24 hours post CTx): - *C1:* in the 7th, 8th, 9th, 10th and 24th hours post CTx, severity reduced 9.1%, 9.1%, 9.1% 4.6% and 4.7% more in IG than CG, respectively. - *C2:* In the 8th, 9th, 10th and 24th hours post CTx, severity reduced 4%, 6.3%, 6.7% and 8.3% more in the CG than IG, respectively. There was no significant difference in the 7th hour post CTx **Mortality** - n=3/37
Muthia 2013 (26)	Design: Control time series Country: Indonesia Data Collection Dates: April 2013 to May 2013	N: 20 Attrition: n=0 Female: n=20 Age: unclear. Cancer: Breast History of CINV: Unclear	Drugs: Cyclophosphamide, Adriamycin-5-fluorouracil Emetogenicity: Not specified Single or multi day: Not specified Commencing Cycle: Not specified Cycle length: Not specified	Ondasentron and dexamethasone	n: 10 Type: Self-prepared ginger infusion (10g fresh Zingiber officanale varietas rubrum [pared and grated] + 100mL water to make. Infused for 15 minutes starting at 90'C, strained and diluted to 150ml. Dose: 1 serve [unclear if 15ml or 150ml] x3/d Duration: Not specified, from the 2nd day after CTx	n: 10 Type: no intervention / standard care	**CINV** INVR (score ranges 0-10; higher score indicates more severe CINV; time point unclear): - IG decrease in score **P=0.000**; CG decrease in score **P=0.011** - Difference between IG and CG **P=0.036** **Mortality** Not reported
Sanaati 2016 (31)	Design: Double blind RCT Country: Iran	N: 43 Attrition: n=13 (30%); n=7 IG; n=5 CG	Drugs: Not specified Emetogenicity: Not specified	Dexamethasone, metoclopramide and aprepitant	n: 23 Type: 0.5g capsule powdered ginger root	n: 20 Type: Standard Care (no ginger)	**CIN** Incidence (self-designed tool; measured every night from 5 days before to 5 days after CTx): - Mean difference between groups 1.5 (S.E. 0.58); **P=0.006** **CIV**

	Recruitment Dates: May 2013 to June 2014	Female: Not specified Age: range 20-60 years Cancer: Breast History of CINV: Yes Reasons for attrition: CTx cancelled, withdrew, not completing data collection, death (numbers per group unclear)	Single or multi day: Single Commencing Cycle: ≥ Cycle 2 Cycle length: ≥2 weeks	(DMA) capsule	Dose: 1g/d (0.5g BD) Duration: 10 days (from 5 days before to 5 days after CTx)		Incidence (self-designed tool; measured every night from 5 days before to 5 days after CTx): - Mean difference between groups 0.11 (S.E. 0.25); **P<0.0001** **Mortality** Not reported
Shokri 2017 (32)	Design: Double blind, placebo RCT Country: Iran Data Collection and Analysis Dates: October 2014 to February 2015	N: 49 Attrition: n=0 Female: n=49 Age: mean 53 ± 11-16 years. Cancer: Stage I to III ovarian cancer who had undergone cytoreductive surgery History of CINV: Not specified	Drugs: Carboplatin and paclitaxel Emetogenicity: Not specified Single or multi day: Not specified Commencing Cycle: Not specified Cycle length: 21 days	Not specified	n: 20 Type: 1g capsule Dose: 2g/d (1g BD) Duration: for 6 Cycles	n: 29 Type: 1g placebo capsule Dose: 2g/d (1g BD) Duration: for 6 Cycles	**CINV** Incidence (time point not specified): - IG n=8/20; CG n=14/29; P=0.57 between groups **Adverse Events** Incidence (measured at the end of treatment up to 12 months after baseline): - *hematologic, renal and digestive complications (unspecified):* IG n=10/20; CG n=21/29; P=0.11 between groups - *weight loss:* IG n=1/20; CG n=1/29; P=0.66 between groups - *peripheral neuropathy:* IG n=3/20; CG n=5/29; P=0.58 between groups - *bone marrow depression:* IG n=2/20; CG n=2/29; P=0.54 between groups - *transient cortical blindness:* IG n=1/20; CG n=0/29; P=0.41 between groups - *peripheral neuropathy:* IG n=3/20; CG n=5/29; P=0.58 between groups **Mortality** Incidence (during 12-month follow up period): - IG n=2/20; CG n=3/29; P=0.68 between groups
Thamlikitkul 2017 (37)	Design: Double blind, placebo-controlled crossover RCT Country: Thailand Recruitment Dates: February 2015 to December 2015	N: 34 Attrition: 0 Female: n=34 Age: mean 49 (range 32-68) years Cancer: Breast History of CINV: Yes	Drugs: Cyclophosphamide and doxorubicin Emetogenicity: High Single or multi day: Not specified Commencing Cycle: Cycle 2 Cycle length: Not specified	Ondansetron and dexamethasone and rescue domperidone or metoclopramide if needed	n: 34 Type: capsuled dry ginger powder Dose: 1g (0.5g BD) Duration: 5 days starting on Day 1 of CTx for one Cycle then crossed over to second group for the next Cycle	n: 34 Type: Placebo capsule Dose: 0.5g BD Duration: 5 days starting on Day 1 of CTx for one Cycle then crossed over to second group for the next Cycle	**CIN** Severity (VAS score; score ranges 0-100; higher score indicates worse symptoms; measured once daily for 5 days starting on day 1 of CTx): - *Maximum Nausea Score:* IG 35.36 (S.E. 4.43); CG 32.17 (S.E. 3.71); difference between groups 3 (95% CI -3-9), P=0.3 - *Acute Nausea Score:* IG 25.00 (S.E. 4.70); CG 23.00 (S.E. 3.40); difference between groups 2 (95%CI -6-9), P=0.64 - *Delayed nausea score:* IG 25.95 (S.E.3.64); CG 23.08 (S.E. 3.12); difference between groups 2.9 (95%CI -2-7.4), P=0.21 **CIV** Incidence (measured once daily for 5 days starting on day 1 of CTx): - IG n=9/34; CG n=10/34; P=0.5 between groups **Fatigue** Incidence of all grades (measured once daily for 5 days starting on day 1 of CTx): - IG n=25/34; CG n=21/34 **Adverse events** Incidence of Grade ≥3 (measured once daily for 5 days starting on day 1 of CTx): - *Febrile Neutropaenia*: IG n=0/34; CG n=1/34 - *Neutropaenia*: IG n=2/34; CG n=1/34 **Mortality** Not reported

Yekta 2012 (33)	Design: Double blind, placebo-RCT Country: Iran Study Duration Dates: July 2009 to December 2009	N: 98 Attrition: n=18 (18%); unclear from which groups. Female: n=80 Cancer: Breast History of CINV: Yes Reasons for attrition: cancelled CTx, withdrew, did not complete data collection, death. Unclear numbers from each group.	Drugs: Not specified Emetogenicity: 84% moderate to high Single or multi day: Single Commencing Cycle: ≥ Cycle 2 Cycle length: ≥ 2 weeks	Kytril or Granisetron hydrochloride tablets and dexamethasone	n: 40 Type: 0.25g ginger root capsules, dry ginger root (5.38mg 6-gingerol, 1.8mg 8-gingerol, 4.19mg 10-gingerol, 0.92mg 6-shagaol) Dose: 1g (0.25g QID) Duration: For 6 days from 3 days before CTx session	n: 40 Type: Placebo capsule Dose: 0.25g QID made with starch Duration: For 6 days from 3 days before CTx session	**CIV** Incidence (mean (SD); measured daily for 6 days starting 3 days before CTx): - *Anticipatory*: IG n=0.5/40 (0.3); CG n=1.5/40 (5.9); **P=0.04** between groups - *Acute*: IG 2.7/40 (1.2); CG n=3.7/40 (2.5); **P=0.04** between groups - *Delayed*: IG 3.3/40 (1.1); CG n=7.9/40 (3.9); **P=0.003** between groups - *Total*: IG 2.3/40 (5.1); CG 7.9/40 (14); **P=0.002** between groups **Adverse Events** Incidence (no time point specified): - *Heartburn Acute:* IG n=5/40; CG n=0/40; P=0.06 between groups - *Heartburn Delayed:* IG n=2/40; CG n=0/40; P=0.5 between groups - *Heartburn Overall (mean of acute and delayed):*[b] IG 4/40; CG 0/40 **Mortality** Not reported

BFI: Brief Fatigue Inventory; CIN: Chemotherapy-induced nausea; CIV: Chemotherapy-induced vomiting; CINV: Chemotherapy-induced nausea and vomiting; CTx: chemotherapy; d: day; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-G: Functional Assessment of Cancer Therapy-General; FLIE: Functional Living Index Emesis; FLIE-5DR: Functional Living Index Emesis 5 Day Recall; INVR: Rhodes Inventory of Nausea, Vomiting and Retching; MAT: Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool; NRS ESAS: Numerical Rating Scale using Edmonton's Symptom Assessment Scale; n: number; QoL: Quality of Life; RCT: Randomised Controlled Trial; VAS: Visual analogue scale.

[a] Data tables not published, therefore data unclear.

[b] This was calculated by review authors to generate a number used for meta analyses.

[c] Information supplied by author.

Table 2. Included studies located in the researchers' previous systematic review (n=5), examining the effect of ginger supplementation on chemotherapy-induced nausea and vomiting incidence and chemotherapy-related outcomes.

Citation	Study Design & Setting	Population	CTx Protocol	Adjuvant Therapies	Intervention Group/s (IG)	Comparator Group/s (CG)	Results
Fahimi 2011 (28)	Design: Double blind crossover placebo RCT Country: Iran Dates: Not specified	N: 50 Attrition: n=14 Female: n=10 Age: mean 50.2 ± 12.2 years Cancer: lung (50%), others not specified History of CINV: Not specified	Drugs: Cisplatin with at least one of: etoposide, docetaxel, gemcitabine, docetaxel, vinorelbine, cyclophosphamide, paclitaxel, doxorubicin, 5-FU, pemetrexed Emetogenicity: Not specified. Single or multi day: Unclear Commencing Cycle: Not specified Cycle length: Not specified	5-HT3 antagonist (granisetrone) and corticostreoid (hydrocortisone)	n: 36 Type: 0.25g capsule, powdered ginger (Zintoma) Dose: 1g (2x 0.25g BD) Duration: 3 days starting on the day of CTx then a 3-week washout period prior to cross over	n: 36 Type: 0.25g placebo capsule composed of lactose. Dose: 1g (2x 0.25g BD Duration: 3 days starting on the day of CTx then a 3-week washout period prior to cross over	**CIN** Incidence (measured 24, 48 and 72hr post CTx): - *Day 1 (Acute Incidence):* IG n=17/36; CG n=21/36; P=0.388 between groups - *Day 2:* IG n=16/36; CG n=19/36; P=0.508 between groups - *Day 3*: IG n=17/36; CG n=18/36; P<0.999 between groups - *Overall Incidence (mean of Day 1-3):*[a] IG n=17/36; CG n=19/36 - *Delayed Incidence (mean of Day 2-3):*[a] IG n=17/36; CG n=19/36 Severity Score (MANE Score; mean (SD); score ranges 1-7; higher score indicated more severe CIN): - *Day 1 (acute severity):* IG 1.75 (2.02); CG 1.36 (1.91); P=0.14 between groups - *Day 2:* IG 1.78 (1.93); CG 1.50 (2.03); P=0.31 between groups - *Day 3:* IG 1.61 (1.93); CG 1.47 (1.92); P=0.73 between groups - *Overall Severity (mean of Day 1-3 scores):*[a] IG 1.71 (1.96); CG 1.44 (1.95) - *Delayed Severity (mean of Day 2-3 scores):*[a] IG 1.7 (1.93); CG 1.49 (1.98) **CIV** Incidence (measured 24, 48 and 72hr post CTx): - *Day 1 (acute incidence):* IG n=21/36; CG n=27/36; P=0.070 between groups - *Day 2:* IG n=27/36; CG n=29/36; P=0.687 between groups - *Day 3:* IG 29/36; CG 28/36; P<0.999 between groups - *Overall Incidence (mean of Day 1-3):*[a] IG n=26/36; CG n=28/36 - *Delayed Incidence (mean of Day 2-3):*[a] IG n=28/36; CG n=29/36

							Severity Score (MANE Score; mean (SD); score ranges 1-7; higher score indicated more severe CIV): - *Day 1:* IG 1.47 (2.18); CG 0.94 (1.77); P=0.14 between groups - *Day 2:* IG 1.03 (1.89); CG 0.83 (1.84); P=0.72 between groups - *Day 3:* IG 0.80 (1.83); CG 0.92 (1.86); P=0.78 between groups **Mortality** Not reported
Manusi-rivithaya 2004 (34)	Design: Double blind crossover RCT Country: Thailand Dates: Not specified	N: 48 Attrition: n=5 Female: n=43 Age: mean 46±10-14 years Cancer: ovary (76%), cervical (23%) History of CINV: Not specified	Drugs: Cisplatin with one of the following agents: cyclophospham ide, ifosfamide, etoposide, bleomycin, 5-fluorouracil Emetogenicity: High Single or multi day: Unclear Commencing Cycle: Not specified Cycle length: Not specified	Metoclopramide (Day 1 30 min before CTx), dexamethasone and lorazepam (Day 1 30 min before and 6 h after CTx)	n: 43 Type: 0.25g capsule, ginger root powder Dose: 1g (0.25g QID) Duration: 5 days then a 3-4 week washout period prior to cross over	n: 43 Type: 0.25g placebo capsule (corn starch) Dose: 1g (0.25g QID) Duration: 5 days then a 3-4 week washout period prior to cross over	**CIN** Severity (VAS Score; mean (SD); score ranges 0-10; higher score indicates more severe CIN; recorded daily on Days 1-5): - *Day 1 (acute severity):* IG 4.32 (3.61); CG 4.31 (3.31); P=0.875 between groups - *Day 2:* IG 4.23 (3.30); CG 3.84 (3.01); P=0.582 between groups - *Day 3:* IG 4.01 (3.65); CG 4.20 (3.71); P=0.865 between groups - *Day 4:* IG 2.67 (3.23); CG 2.99 (3.30); P=0.294 between groups - *Day 5:* IG 2.14 (2.89); CG 1.89 (2.73); P=0.554 between groups - *Overall Severity (mean of Day 1-5 scores):*[a] IG 3.47 (3.34); CG 3.45 (3.21) - *Delayed Severity (mean of Day 2-5 scores):*[a] IG 3.26 (3.27); CG 3.23 (3.19) **CIV** Incidence (recorded daily on Days 1-5) - >5 episodes: IG n=8/43; CG n=9/43; P=0.754 - 3-5 episodes: IG n=4/42; CG n=5/43; P=0.754 - 1-2 episodes: IG n=15/43; CG n=11/43; P=0.754 - *Overall Incidence (sum of 1->5 episodes):*[a] IG 27/43; CG 25/43 **Side Effects** Incidence:

							- *Any relatable side effects*: IG n=12/43; CG n=8/43; P=0.503 between groups - *Restlessness*: IG n=8/46; n=CG 2/46; P=0.109 between groups - *Diarrhoea*: IG n=2/46; CG n=6/46; P=0.289 between groups - *Constipation*: IG n=6/46; CG n=3/46; P=0.508 between groups - *Headache*: IG n=3/46; CG n=1/46; P=0.625 between groups - *Dizziness*: IG n=5/46; CG n=6/46; P=1.000 between groups - *Heartburn*: IG n=3/46; CG n=3/46; P=1.000 between groups - *Palpitation*: IG n=1/46; CG n=1/46; P=1.000 between groups - *Akathisia*: IG n=1/46; CG n=0/46 - *Acute Dystonic Reaction:* CG n=1/46; CG n=0/46 **Mortality** Not reported
Panahi 2012 (29)	Design: Open pilot RCT Country: Iran Study Duration Dates: July 2008 to November 2009	N: 100 Attrition: n=22 Female: n=78 Age: mean 58.1±9.2 years Cancer: Mainly advanced breast History of CINV: Not specified	Drugs: Predominately TEC (docetaxel, epirubicin, cyclophosphamide) Emetogenicity: Moderate or High Single or multi day: Not specified Commencing Cycle: Mainly Cycle 1	Standard antiemetic regimen (granisetron and dexamethasone)	n: 37 Type: 0.5g capsule powdered ginger root Dose: 1.5g (0.5g TID) Duration: 5 days from the day of CTx. Number of Cycles unspecified	n: 41 Type: Usual care	**CIN** Incidence: - *<6 hours*: IG n=9/37; CG n=17/41; P=0.11 between groups - *6-24 hours*: IG n=13/37; CG n=24/41; **P=0.04** between groups - *Day 2*: IG n=17/37; CG n=22/41; P=0.43 between groups - *Day 3*: IG n=20/37; CG n=22/41; P=0.93 between groups - *Day 4*: IG n=21/37; CG n=19/41; P=0.42 between groups - *Overall Incidence (mean of <6hrs, 6-24hrs and Day 2-4):*[a] IG n=16/37; CG n=21/41 - *Acute Incidence (mean of <6hrs and 6-24hrs):*[a] IG n=11/37; CG n=21/41 - *Delayed Incidence (mean of Day 2-4):*[a] IG n=19/37; CG n=31/57 **CIV** Incidence (combined with retching): - *<6 hours*: IG n=9/37; CG n=11/41; P=0.80 between groups

			Cycle length: Not specified				- *6-24 hours*: IG n=7/37; CG n=12/41; P=0.26 between groups - *Day 2:* IG n=13/37; CG n=11/41; P=0.47 between groups - *Day 3*: IG n=13/37; CG n=12/41; P=0.63 between groups - *Day 4:* IG n=16/37; CG n=14/41; P=0.46 between groups - *Overall Incidence (mean of <6hrs, 6-24hrs and Day 2-4):*[a] IG 12/37; CG 12/41 - *Acute Incidence (mean of <6hrs and 6-24hrs):*[a] IG n=8/37; CG n=12/41 - *Delayed Incidence (mean of Day 2-4):*[a] IG n=14/37; CG n=12/57 **CINV** RINVR (Mean Score (SD); score ranges 0-24; higher score indicates more severe CINV): - *<6 hours*: IG 3.22 (4.45); CG 2.98 (3.95); P=0.80 between groups - *6-24 hours*: IG 3.11 (4.04); CG 4.10 (4.42); P=0.31 between groups - *Day 2*: IG 4.35 (4.84); CG 4.32 (4.36); P=0.98 between groups - *Day 3*: IG 4.78 (4.82); CG 4.22 (5.06); P=0.62 between groups - *Day 4*: IG 5.70 (5.60); CG 4.47 (5.45); P=0.33 between groups **Mortality** Not reported
Ryan 2012 (27)	Design: Double blind, placebo RCT Country: USA Recruitment Dates: June 2002 to December 2008	N: 371 Attrition: n=88 (IG n=49; CG n=39) Female: n=257 Age: mean 53-54 (S.E. 1) Cancer: Breast (56%);	Drugs: Not specified Emetogenicity: Any Single or multi day: Not specified Commencing Cycle: ≥ Cycle 2 Cycle length: Not specified	5-HT3 receptor antagonist. dexamathasone at all CTx Cycles	n: 134 Type 1: 0.25g capsule ginger liquid extract of ginger root (8.5mg of combined gingerols, zingerone and shogoal) with olive oil containing other unspecified excipients to improve solubilisation and	n: 149 Type: 0.25g placebo capsule with olive oil and excipients Dose: 1.5g (3x0.25g BD) Duration: 6 days, starting three days before CTx.	**CIN** Severity Score (LS mean change (SE); score ranges 1-7; higher score indicated more severe CIN; measured at 4 times daily from Days 1-4 of each Cycle): - *Average Nausea All IG's vs CG:* -0.350 (-0.140); **P=0.013** - *Average Nausea*: IG -0.441 (0.127); CG 0.015 (0.121); **P=0.046** between groups **Quality of Life** FACIT-G Score (score ranges 0-108; higher score indicates better QoL; measured at Day 1 and Day 4 of each Cycle): - no significant difference between groups

		GI (7%); lung (5%) History of CINV: Yes			increase bioavailability Type 2: Placebo capsule with olive oil and excipients Dose: 0.5g/d (0.25g and x4 placebo) Duration: 6 days, starting three days before CTx		**Adverse Events** Time point not specified: - n=24/745 (all four groups). Related to study intervention (n=9/557) (GI symptoms: Grade 2 heartburn, bruising/flushing, rash; not delineated between treatment doses) - Gastrointestinal symptoms: IG n=5/183; CG n=5/188 **Mortality** Not reported
		N: 375 Attrition: n=95 (IG n=49; CG n=46) Female: n=257 Age: mean 52-53 (S.E. 1) Cancer: Breast (56%); GI (6%); gynecologic (5%) History of CINV: Yes	As per above	As per above	n: 141 Type 1: 0.25g capsule ginger liquid extract of ginger root (8.5mg of combined gingerols, zingerone and shogoal) with olive oil containing other unspecified excipients to improve solubilisation and increase bioavailability Type 2: Placebo capsule with olive oil and excipients Dose: 1g/d of ginger (x4 0.25g and x2 placebo) Duration: 6 days, starting three days before CTx	As per above.	**CIN** Severity Score (score ranges 1-7; higher score indicated more severe CIN; measured at 4 times daily from days 1-4 of each Cycle): - *Average Nausea*: IG LS Mean Change -0.402, SE 0.124; CG 0.015, SE 0.121; P=0.076 between groups **Quality of Life** FACIT-G Score (score ranges 0-108; higher score indicates better QoL; measured at day 1 and day 4 of each Cycle): **-** no significant difference between groups **Adverse Events** Time point not specified: - n=24/745 (all four groups). Related to study intervention (n=9/557) (GI symptoms: Grade 2 heartburn, bruising/flushing, rash; not delineated between treatment doses) - Gastrointestinal symptoms: IG n=7/187; CG n=5/188 **Mortality** Not reported

		N: 375 Attrition: n=74 (IG n=35; CG n=39) Female: n=277 Age: mean 52-53 (S.E. 1) Cancer: Breast (60%); GI (6%); lung (5%) History of CINV: Yes	As per above	As per above	n: 152 Type 1: 0.25g capsule ginger liquid extract of ginger root (8.5mg of combined gingerols, zingerone and shogoal) with olive oil containing other unspecified excipients to improve solubilisation and increase bioavailability Dose: 1.5g/d (x6 0.25g; no placebo). Duration: 6 days, starting three days before CTx	As per above.	**CIN** Severity Score (score ranges 1-7; higher score indicated more severe CIN; measured at 4 times daily from Days 1-4 of each Cycle): - *Average Nausea*: IG C LS Mean Change -0.158, SE 0.120; CG 0.015, SE 0.121; P=0.738 between groups **Quality of Life** FACIT-G Score (score ranges 0-108; higher score indicates better QoL; measured at day 1 and day 4 of each Cycle): - no significant difference between groups **Adverse Events** Time point not specified: - n=24/745 (all four groups). Related to study intervention (n=9/557) (GI symptoms: Grade 2 heartburn, bruising/flushing, rash; not delineated between treatment doses) - Gastrointestinal symptoms: IG n=9/187; CG n=5/188 **Mortality** Not reported
Zick 2009 (38)	Design: Double blind Placebo RCT Country: USA Study Duration Dates: June 2003 and May 2006	N: 110 Attrition: n=21 (IG n=10; GC n=11) Female: n=92 Age: mean 53-55±11-12 years Cancer: Not specified	Drugs: 20 different regimens specified in publication Emetogenicity: 17% high; 65% moderate. Single or multi day: Single Commencing Cycle: ≥ Cycle 2	Apripetant, 5-HT3 receptor antagonist (Dolasetron, Granistron, Ondansetron or Palonosetron)	n: 53 Type: 0.25g capsule dry extract of ginger root (10:1 (v/v) extraction solvent (ethanol 50%)/root) standardized to 15 mg (5%) of total gingerols. 5.38 mg (2.15%) 6-gingerol, 1.80 mg (0.72%) 8-gingerol, 4.19 mg (1.78%) 10-gingerol, and 0.92	n: 57 Type: Placebo capsules with lactose powder Dose: 8/day Duration: 3 days starting on day of CTx administration	**CIN** Incidence: - *<24hr post CTx (acute incidence):* IG n=33/53; CG n=31/57; P=0.86 between groups - *24-48hr post CTx (delayed incidence):* IG n=37/53; CG n=31/57; P=0.16 between groups - *Overall (mean of <24hrs and 24-48hrs):*[a] IG n=35/53; CG n=31/57 Severity (MANE Score; mean (SD); score ranges 1-7; higher score indicated more severe CIN): - *<24hr post CTx, no aprepitant:* IG 3.1 (1.2) CG 2.8 (1.3); P=0.47 - *<24hr post CTx, aprepitant:* IG 2.8 (1.1); CG 3.1 (1.5); P=0.55

		History of CINV: Yes	Cycle length: Not specified		mg (0.37%) 6-shogaol. AND placebo capsules. Dose: 1g/d (4x 0.25g + 4x placebo) Duration: 3 days starting on day of CTx administration		- *24-48hr post CTx, no aprepitant:* IG 3.0 (1.1); CG 3.0 (1.3); P=0.69 - *24-48hr post CTx, aprepitant:* IG 2.9 (1.3); CG 2.2 (0.7); **P=0.01** - *Overall (mean of <24hr and 24-48hr scores):*[a] IG 2.95 (1.18); CG 2.78 (1.2) - *Acute Severity (mean of <24hr scores):*[a] IG 2.95 (1.15); CG 2.95 (1.4) - *Delayed Severity (mean of 24-48hr scores):*[a] IG 2.95 (1.2); CG 2.6 (1) **CIV** Incidence: - **<***24hr post CTx (acute incidence):* IG n=19/53; CG n=14/57; P=0.47 between groups - *24-48hr post CTx (delayed incidence):* IG n=19/53; CG n=9/57; P=0.07 between groups - *Overall Incidence (mean of <24hrs and 24-48hrs):*[a] IG n=19/53; CG n=12/57 Severity (MANE Score; mean (SD); score ranges 1-7; higher score indicated more severe CIV): - *24hr post CTx, no aprepitant:* IG 3.1 (1.4); CG 3.6 (1.4); P=0.61 - *24hr post CTx, aprepitant:* IG IG 3.4 (0.6); CG 4.0 (1.7); P=0.91 - *24-48hr post CTx, no aprepitant:* IG 2.7 (0.9); CG 4.0 (1.3); P=0.88 - *24-48hr post CTx, aprepitant:* IG 3.0 (1.4); CG 3.0 (0.0); P=0.77 **Adverse Events** Occurring within the 3-day study period: - *Fatigue:* IG n=1/53; CG n=5/57; **P=0.03** - *Laboratory abnormalities:* IG n=8/53; CG n=8/57; P=0.06 - *Miscellaneous:* IG n=3/53; CG n=8/57; **P=0.02** **Mortality** Not reported
		N: 109 Attrition: n=23 (IG	As per above.	As per above	n: 52	As per above	**CIN** Incidence:

		n=12; GC n=11) Female: n=83 Age: mean 55-58±11-12 years Cancer: Not specified History of CINV: Yes	Emetogenicity: 19% high; 63% moderate		Type: As per above, no placebo. Dose: 2g/d (8x 0.25g) Duration: 3 days starting on day of CTx administration		- *<24hr post CTx (acute incidence):* IG n=30/52; CG n=31/57; P=0.86 between groups - *24-48hr post CTx (delayed incidence):* IG n=27/52; 31/57; P=0.16 between groups - *Overall (mean of <24hrs and 24-48hrs):*[a] IG n=29/52; CG n=31/57 Severity (MANE Score; mean (SD); score ranges 1-7; higher score indicated more severe CIN): - *<24hr post CTx, no aprepitant:* IG 3.0 (1.1); CG 2.8 (1.3); P=0.47 - *<24hr post CTx, aprepitant:* IG 2.8 (1.5); CG 3.1 (1.5); P=0.55 - *24-48hr post CTx, no aprepitant:* IG 3.2 (1.1); CG 3.0 (1.3); P=0.69 - *24-48hr post CTx, aprepitant:* IG 3.9 (0.9); CG 2.2 (0.7); **P=0.01** - *Overall (mean of <24hr and 24-48hr scores):*[a] IG 3.23 (1.15); CG 2.78 (1.2) - *Acute Severity (mean of <24hr scores):*[a] IG 2.9 (1.3); CG 2.95 (1.4) - *Delayed Severity (mean of 24-48hr scores):*[a] IG 3.55 (1); CG 2.6 (1) **CIV** Incidence: - *24hr post CTx (acute incidence):* IG n=17/53; CG n=14/57; P=0.47 between groups - *24-48hr post CTx (delayed incidence)*: IG n=12/53; CG n=9/57; P=0.07 between groups - *Overall Incidence (mean of <24hrs and 24-48hrs):*[a] IG n=15/53; CG n=12/57 Severity (MANE Score; mean (SD); score ranges 1-7; higher score indicated more severe CIV): - *24hr post CTx, no aprepitant:* IG 2.9 (0.9); CG 3.6 (1.4); P=0.61 - *24hr post CTx, aprepitant:* IG 3.7 (1.5); CG 4.0 (1.7); P=0.91 - *24-48hr post CTx, no aprepitant:* IG 3.7 (1.0); CG 4.0 (1.3); P=0.88 - *24-48hr post CTx, aprepitant:* IG 3.6 (1.3); CG 3.0 (0.0); P=0.77 **Adverse Events** Occurring within the 3-day study period: - *Fatigue:* IG n=0/52; CG n=5/57; **P=0.03** between groups

							- *Laboratory abnormalities:* IG n=1/52; CG n=8/57; P=0.06 between groups - *Miscellaneous:* IG n=1/52; CG n=8/57; **P=0.02** between groups **Mortality** Not reported

CIN: chemotherapy induced nausea; CIV: chemotherapy induced vomiting; CINV: chemotherapy induced nausea and vomiting; CTx: chemotherapy; ESAS: Edmonton's Symptom Assessment Scale; FACT-G: Functional Assessment of Cancer Therapy-General; GI: gastrointestinal; LS Mean: least squares mean; MANE: Morrow Assessment of Nausea and Emesis; N: number; RCT: Randomised Controlled Trial; RINVR: Rhodes Index of Nausea, Vomiting, and Retching; VAS: Visual Analogue Score

[a] This was calculated by review authors to generate a number used for meta analyses.

Online Supplementary Material 4: Non-significant meta-analyses forest plots examining the efficacy and safety of ginger for ameliorating chemotherapy-induced nausea and vomiting

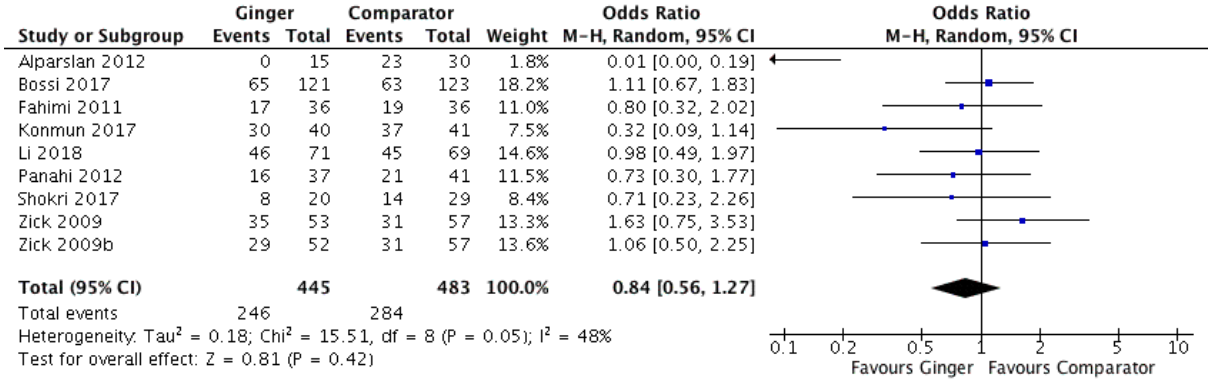

Figure 1. Ginger supplementation of any dose or duration had no association with likelihood of overall nausea (OR: 0.84, 95% CI: 0.56-1.27; P=0.42; n=8 studies; n=9 interventions; n=928 participants; I^2=48%).

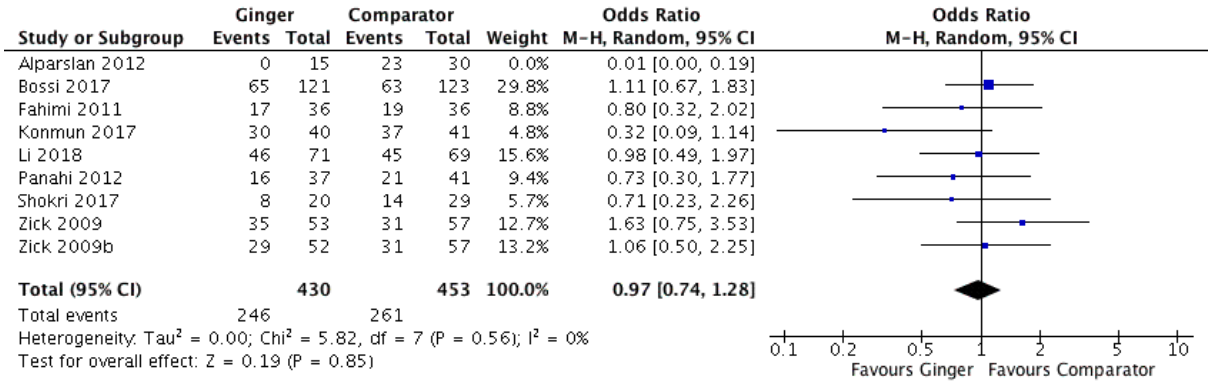

Figure 2. Ginger supplementation of any dose or duration had no association with likelihood of overall nausea (OR: 0.97, 95% CI: 0.74-1.28; P=0.82; n=7 studies; n=8 interventions; n=883 participants; I^2=0%; GRADE level: moderate). Sensitivity analysis: studies with high risk of bias (>70% of Cochrane Risk of Bias domains rated as unclear or high risk of bias) deselected; sensitivity analysis according to dose (≤/>1g/day) or duration (≤/>3 days) did not result in significant findings.

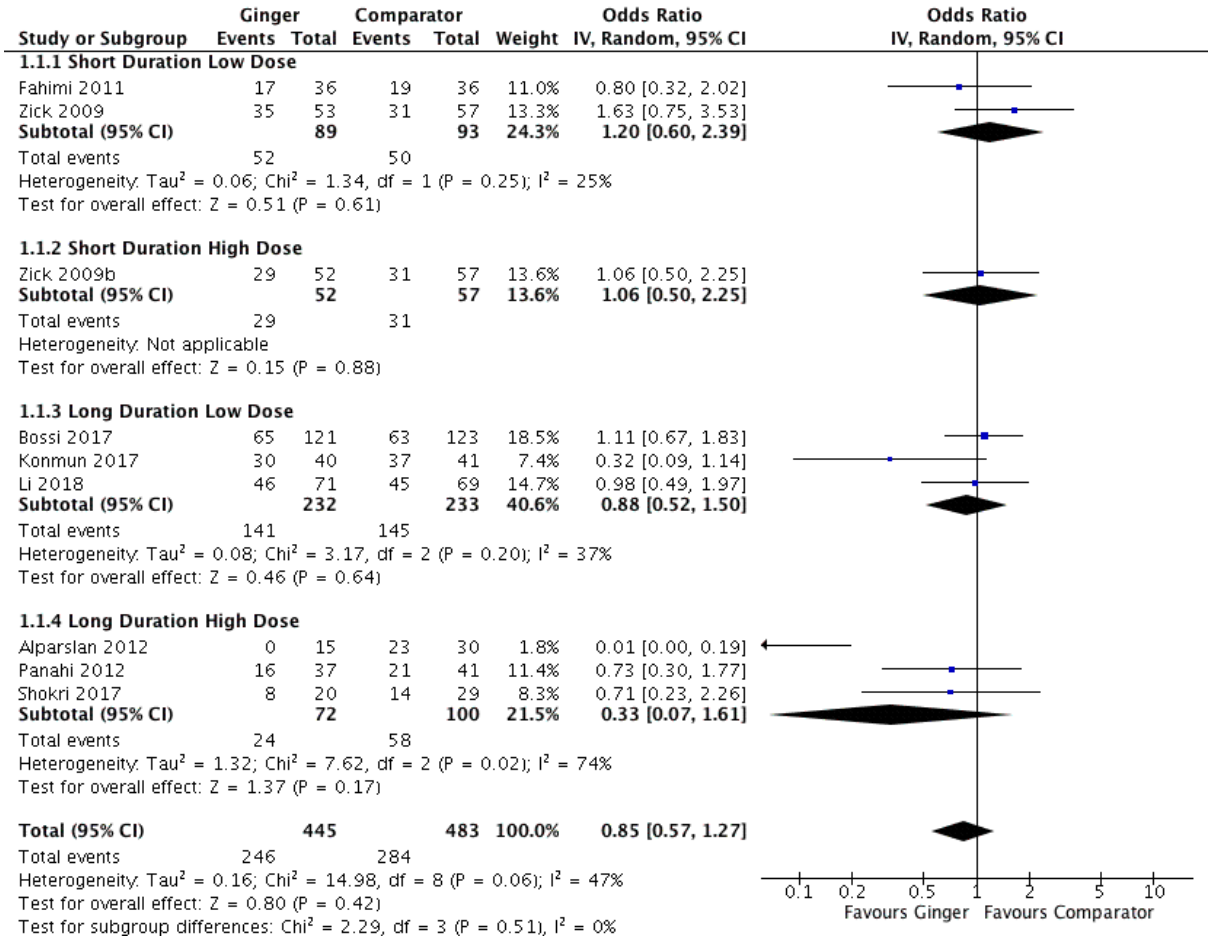

Figure 3. Ginger supplementation of any dose or duration had no association with likelihood of overall nausea with subgroup analysis using the four categories outlined in the meta-analysis method of varied duration and dosage (OR: 0.85, 95% CI: 0.57-1.27; P=0.51; n=7 studies; n=8 interventions; n=928 participants; I^2=47%).

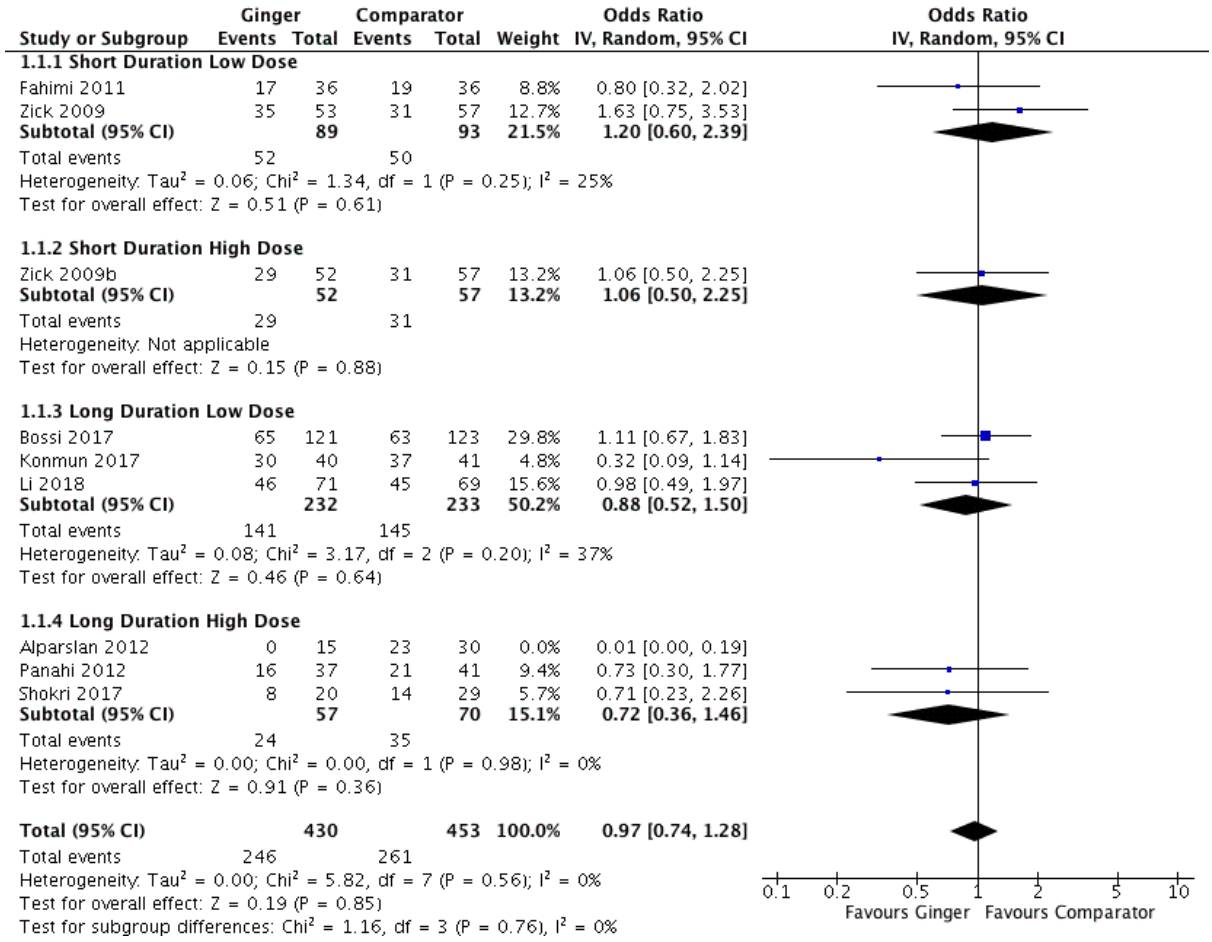

Figure 4. Ginger supplementation of any dose or duration had no association with likelihood of overall nausea with subgroup analysis using the four categories outlined in the meta-analysis method of varied duration and dosage (OR: 0.97, 95% CI: 0.74-1.28; P=0.76; n=7 studies; n=8 interventions; n=883 participants; I^2=0%). Sensitivity analysis: studies with high risk of bias (>70% of Cochrane Risk of Bias domains rated as unclear or high risk of bias) deselected.

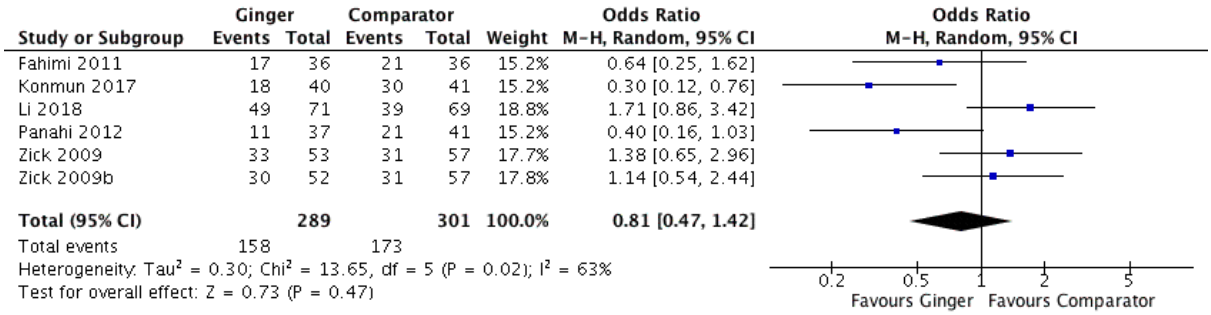

Figure 5. Ginger supplementation of any dose or duration had no association with likelihood of acute nausea (OR: 0.81, 95% CI: 0.47-1.42; P=0.47; n=5 studies; n=6 interventions; n=590 participants; I^2=63%; GRADE level: very low). Sensitivity analysis according to dose (≤/>1g/day) or duration (≤/>3 days) did not result in significant findings.

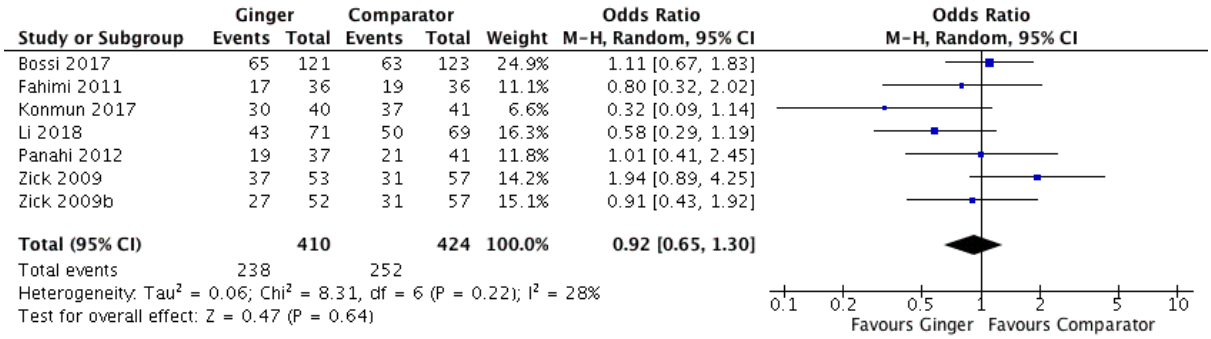

Figure 6. Ginger supplementation of any dose or duration had no association with likelihood of delayed nausea (OR: 0.92, 95% CI: 0.65-1.30; P=0.64; n=6 studies; n=7 interventions; n=834 participants; I^2=28%; GRADE level: moderate). Sensitivity analysis according to dose (≤/>1g/day) or duration (≤/>3 days) did not result in significant findings.

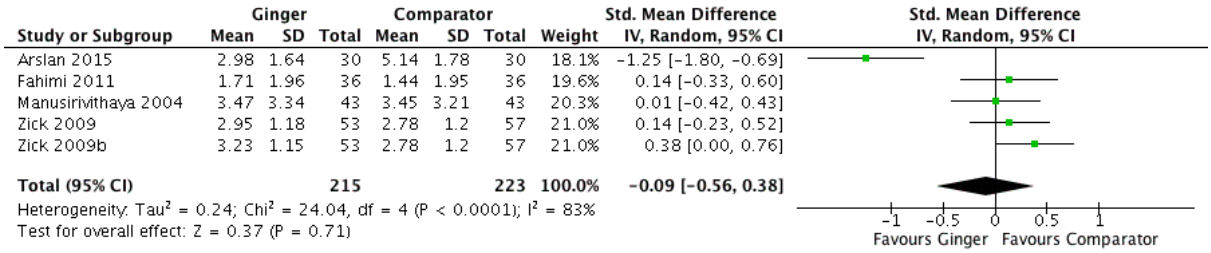

Figure 7. Ginger supplementation of any dose or duration had no association with overall nausea severity (SMD: -0.09, 95% CI: -0.56-0.38; P=0.71; n=4 studies; n=5 interventions; n=438 participants; I^2=83%).

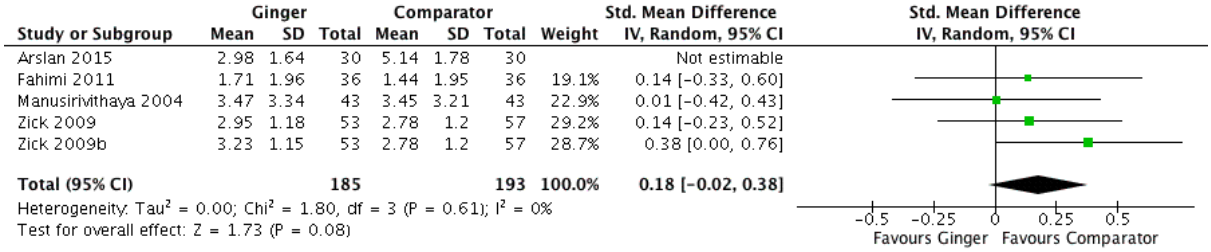

Figure 8. Ginger supplementation of any dose for any duration had no association with overall nausea severity (SMD: 0.18, 95% CI: -0.02-0.38; P=0.08; n=3 studies; n=4 interventions; n=378 participants; I^2=0%; GRADE level: low). Sensitivity analysis: studies with high risk of bias (>70% of Cochrane Risk of Bias domains rated as unclear or high risk of bias) deselected; sensitivity analysis according to dose (≤/>1g/day) or duration (≤/>3 days) did not result in significant findings.

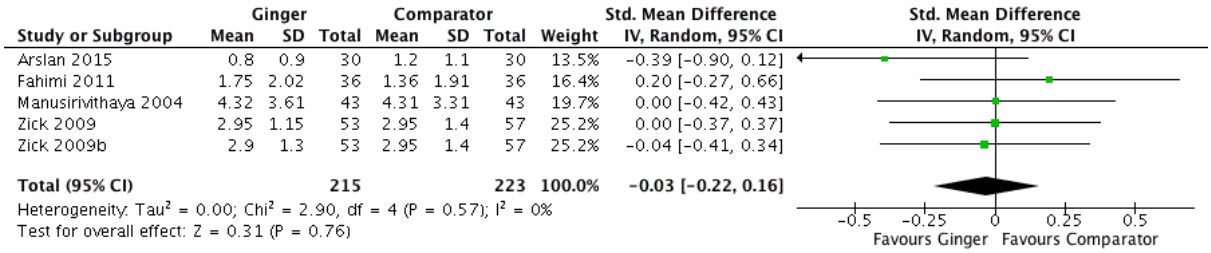

Figure 9. Ginger supplementation of any dose or duration had no association with acute nausea severity (SMD: -0.03, 95% CI: -0.22-0.16; P=0.76; n=4 studies; n=5 interventions; n=438 participants; I^2=0%).

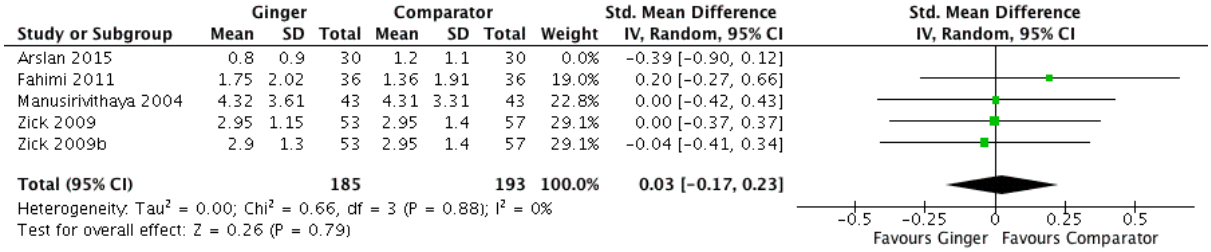

Figure 10. Ginger supplementation of any dose or duration had no association with acute nausea severity (SMD: 0.03, 95% CI: -0.17-0.23; P=0.79; n=3 studies; n=4 interventions; n=378 participants; I^2=0%; GRADE level: low). Sensitivity analysis: studies with high risk of bias (>70% of Cochrane Risk of Bias domains rated as unclear or high risk of bias) deselected; sensitivity analysis according to dose (≤/>1g/day) or duration (≤/>3 days) did not result in significant findings.

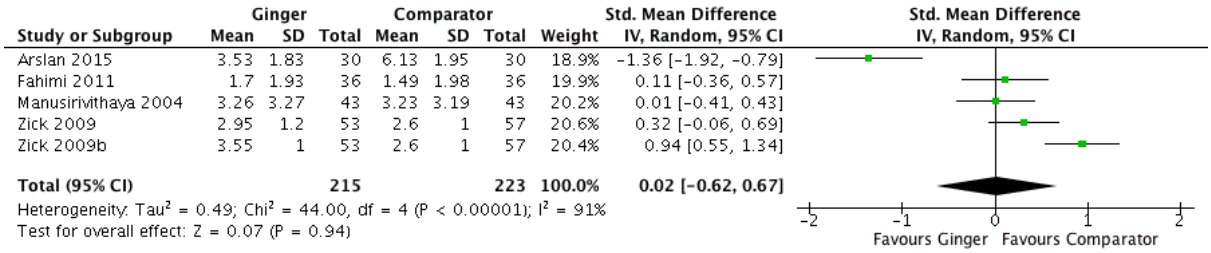

Figure 11. Ginger supplementation of any dose or duration had no association with delayed nausea severity (SMD: 0.02, 95% CI: -0.62-0.67; P=0.94; n=4 studies; n=5 interventions; n=438 participants; I^2=91%).

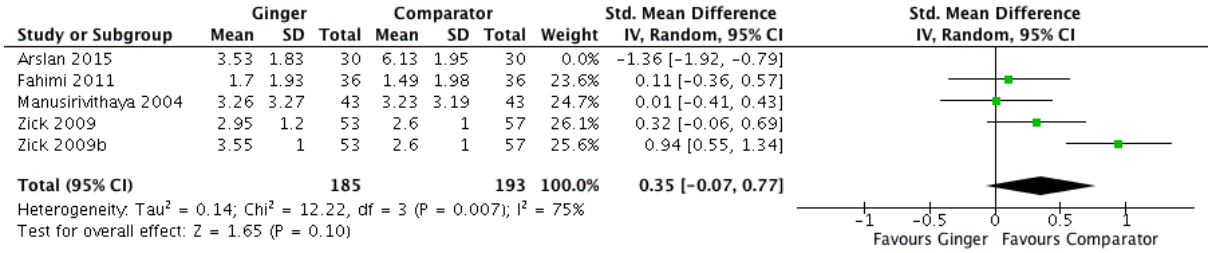

Figure 12. Ginger supplementation of any dose or duration had no association with delayed nausea severity (SMD: 0.35, 95% CI: -0.07-0.77; P=0.10; n=3 studies; n=4 interventions; n=378 participants; I^2=75%; GRADE level: very low). Sensitivity analysis: studies with high risk of bias (>70% of Cochrane Risk of Bias domains rated as unclear or high risk of bias) deselected.

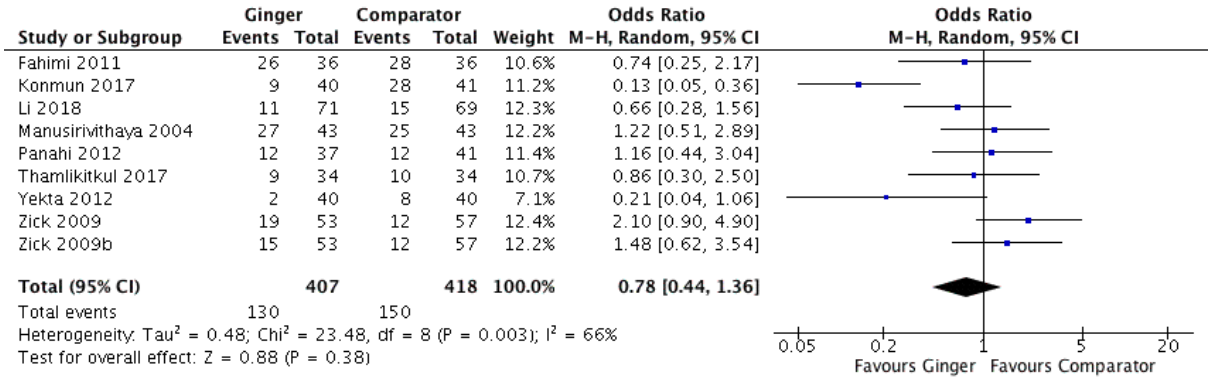

Figure 13. Ginger supplementation of any dose or duration had no association with likelihood of overall vomiting (OR: 0.78, 95% CI: 0.44-1.36; P=0.38; n=8 studies; n=9 interventions; n=825 participants; I^2=66%; GRADE level: very low).

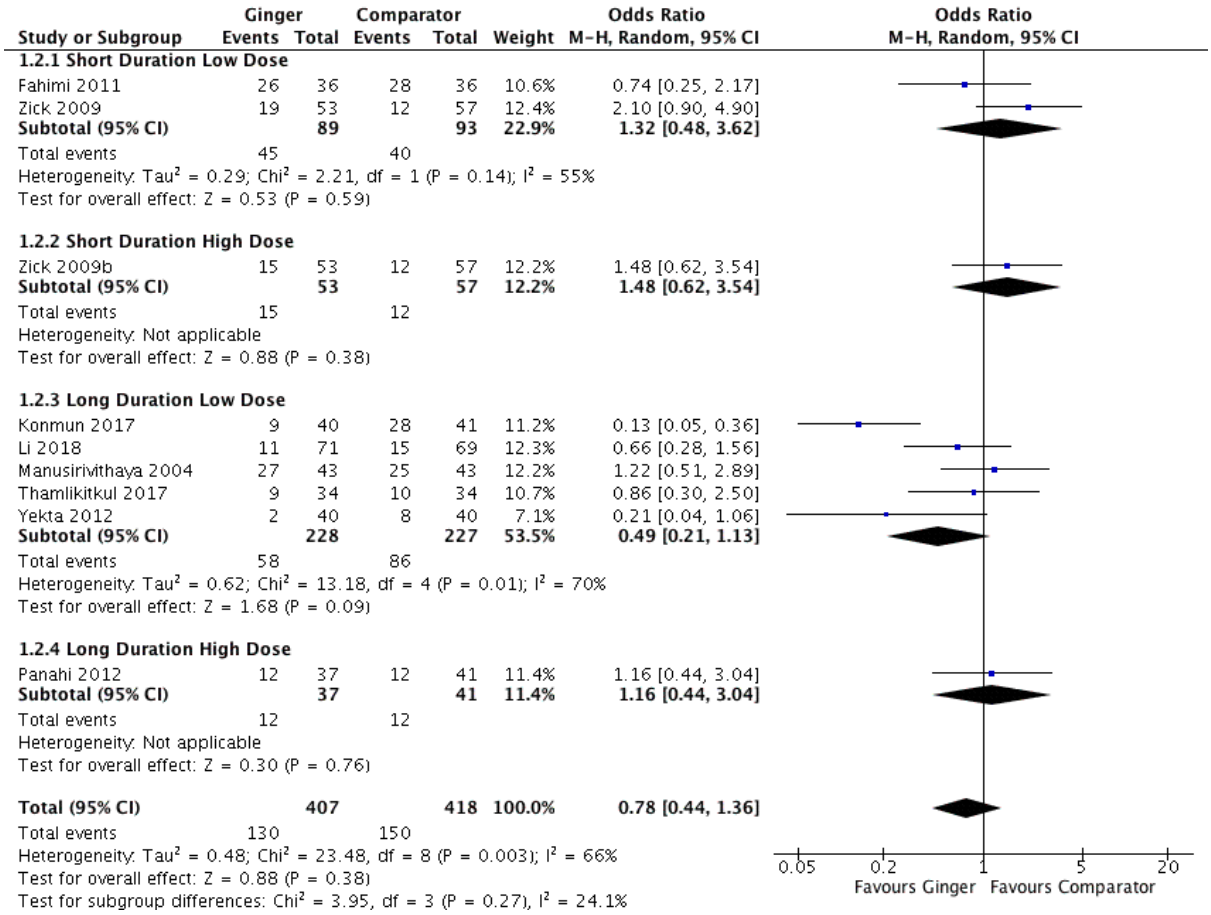

Figure 14. Ginger supplementation of varying dose and duration had no association with likelihood of overall vomiting with subgroup analysis (OR: 0.78, 95% CI: 0.44-1.36; P=0.27; n=8 studies; n=9 interventions; n=825 participants; I^2=66%).

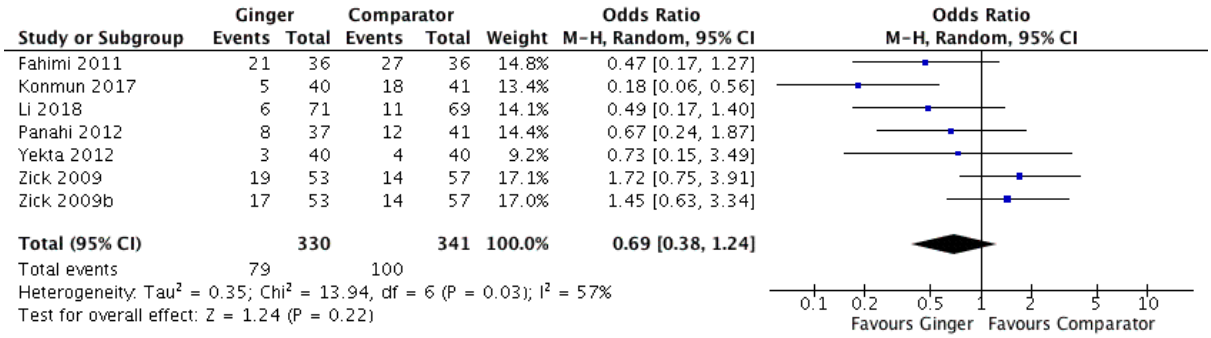

Figure 15. Ginger supplementation of any dose or duration had no association with likelihood of acute vomiting (OR: 0.69, 95% CI: 0.38-1.24; P=0.22; n=6 studies; n=7 interventions; n=671 participants; I^2=57%; GRADE level: very low).

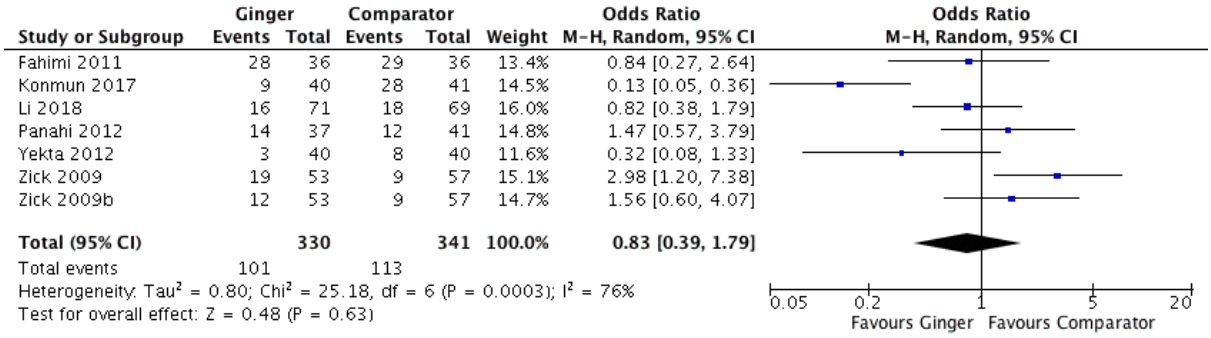

Figure 16. Ginger supplementation of any dose or duration had no association with likelihood of delayed vomiting (OR: 0.83, 95% CI: 0.39-1.79; P=0.63; n=6 studies; n=7 interventions; n=671 participants; I^2=76%; GRADE level: very low).

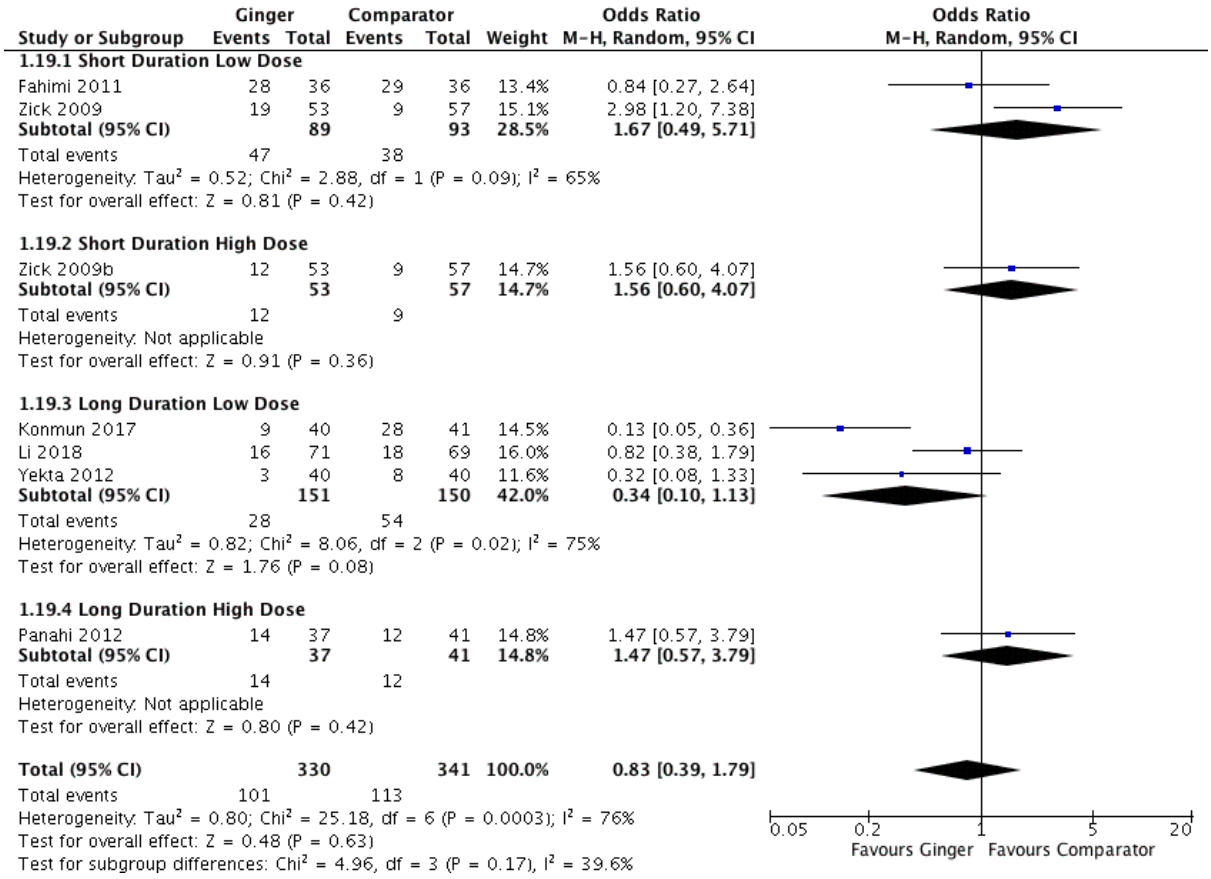

Figure 17. Ginger supplementation of varying dose and duration had no association with likelihood of delayed vomiting with subgroup analysis (OR: 0.83, 95% CI: 0.39-1.79; P=0.17; n=6 studies; n=7 interventions; n=671 participants; I^2=76%).

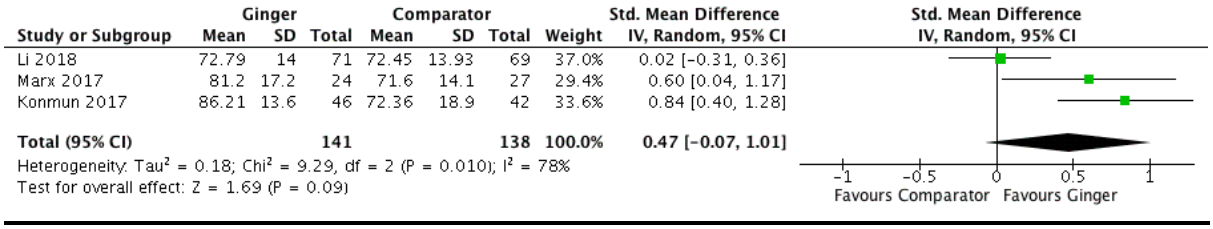

Figure 18. Ginger supplementation of any dose for any duration had no association with quality of life (SMD: 0.47, 95% CI: -0.07-1.01; P=0.09; n=3 studies; n=3 interventions; I^2=78%; n=279 participants; GRADE level: low).

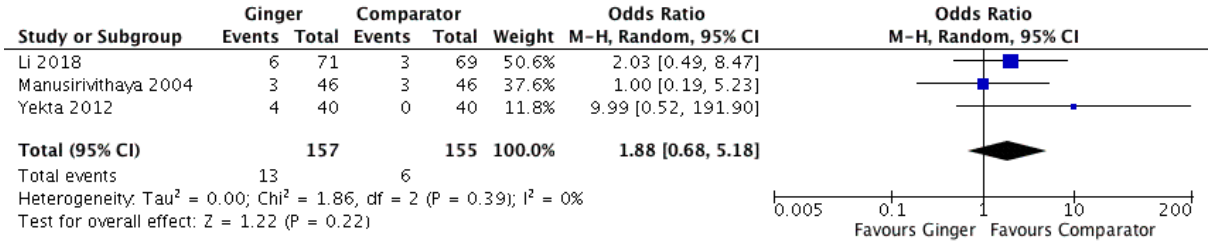

Figure 19. Ginger supplementation of any dose for any duration had no association with likelihood of heartburn (OR: 1.88, 95% CI: 0.68-5.18; P=0.22; n=3 studies; n=3 interventions; n=312 participants; I^2=0%; GRADE level: low).

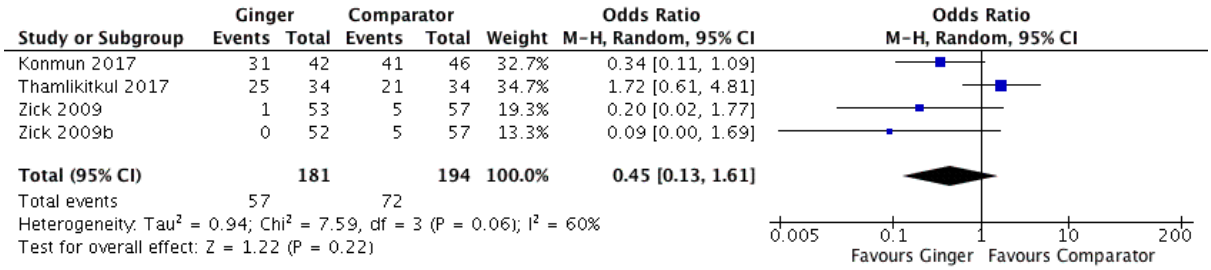

Figure 20. Ginger supplementation of any dose for any duration had no association with likelihood of fatigue (OR: 0.45, 95% CI: 0.13-1.61; P=0.22; n=3 studies; n=4 interventions; n=375 participants; I^2=60%).

Online Supplementary Material 4: GRADE Assessment

Table 1. GRADE assessment of ginger supplementation compared to placebo or standard care for chemotherapy-induced nausea and vomiting and related outcomes.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ginger**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Nausea Overall Incidence - Sensitivity Analysis (low risk of bias only, any duration, any dose) – Figure 2 of Online Supplementary Material 4											
8 interventions (n=7 studies)	randomised trials	not serious	not serious	not serious	serious [d]	none	246/430 (57.2%)	261/453 (57.6%)	**OR 0.97** (0.74 to 1.28)	**7 fewer per 1,000** (from 75 fewer to 59 more)	⊕⊕⊕◯ MODERATE
Nausea Acute Incidence (any duration, any dose) – Figure 5 of Online Supplementary Material 4											
6 interventions (n=5 studies)	randomised trials	serious [b]	serious [c]	not serious	serious [d]	none	158/289 (54.7%)	173/301 (57.5%)	**OR 0.81** (0.47 to 1.42)	**52 fewer per 1,000** (from 186 fewer to 83 more)	⊕◯◯◯ VERY LOW
Nausea Delayed Incidence (any duration, any dose) – Figure 6 of Online Supplementary Material 4											
7 interventions (n=6 studies)	randomised trials	not serious	not serious	not serious	serious [d]	none	238/410 (58.0%)	252/424 (59.4%)	**OR 0.92** (0.65 to 1.30)	**20 fewer per 1,000** (from 107 fewer to 61 more)	⊕⊕⊕◯ MODERATE
Nausea Overall Severity - Sensitivity Analysis (low risk of bias only, any duration, any dose) – Figure 8 of Online Supplementary Material 4											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ginger**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
4 interventions (n=3 studies)	randomised trials	not serious	not serious	not serious	very serious [a]	none	142	150	-	SMD **0.18 higher** (0.02 lower to 0.38 higher)	⊕⊕◯◯ LOW
Nausea Acute Severity - Sensitivity Analysis (low risk of bias only, any duration, any dose) – Figure 10 of Online Supplementary Material 4											
4 interventions (n=3 studies)	randomised trials	not serious	not serious	not serious	very serious [a]	none	185	193	-	SMD **0.03 SD higher** (0.17 lower to 0.23 higher)	⊕⊕◯◯ LOW
Nausea Delayed Severity - Sensitivity Analysis (low risk of bias only, any duration, any dose) – Figure 12 of Online Supplementary Material 4											
4 interventions (n=3 studies)	randomised trials	not serious	serious [c]	not serious	very serious [a]	none	185	193	-	SMD **0.35 SD higher** (0.07 lower to 0.77 higher)	⊕◯◯◯ VERY LOW
Vomiting Overall Incidence (any duration, any dose) – Figure 13 of Online Supplementary Material 4											
9 interventions (n=8 studies)	randomised trials	not serious	serious [c]	not serious	very serious [d]	none	130/407 (31.9%)	150/418 (35.9%)	**OR 0.78** (0.44 to 1.36)	**55 fewer per 1,000** (from 163 fewer to 74 more)	⊕◯◯◯ VERY LOW
Vomiting Acute Incidence (any duration, any dose) – Figure 15 of Online Supplementary Material 4											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ginger**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
7 interventions (n=6 studies)	randomised trials	serious [q]	serious [e]	not serious	very serious [d]	none	79/330 (23.9%)	100/341 (29.3%)	**OR 0.69** (0.38 to 1.24)	**71 fewer per 1,000** (from 157 fewer to 47 more)	⊕◯◯◯ VERY LOW
Vomiting Acute Incidence – Subgroup Analysis (>3-days duration, ≤1g/day) – Figure 3 of Manuscript											
3 interventions (n=3 studies)	randomised trials	not serious	not serious	not serious	serious [a]	none	14/151 (9.3%)	33/150 (22.0%)	**OR 0.37** (0.17 to 0.81)	**126 fewer per 1,000** (from 174 fewer to 34 fewer)	⊕⊕⊕◯ MODERATE
Vomiting Delayed Incidence (any duration, any dose) – Figure 16 of Online Supplementary Material 4											
7 interventions (n=6 studies)	randomised trials	serious [s]	serious [e]	not serious	serious [a]	none	101/330 (30.6%)	113/341 (33.1%)	**OR 0.83** (0.39 to 1.79)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⊕◯◯◯ VERY LOW
Quality of Life Score (any duration, any dose) – Figure 18 of Online Supplementary Material 4											
3 interventions (n=3 studies)	randomised trials	not serious	serious [c]	not serious	serious [a]	none	117	111	-	SMD **0.47 SD higher** (0.07 lower to 1.01 higher)	⊕⊕◯◯ LOW
Fatigue Incidence (Sensitivity Analysis - ≤3-days, any dose) – Figure 4 of Manuscript											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ginger**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
2 interventions (n=1 study)	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/105 (1.0%)	10/114 (8.8%)	**OR 0.15** (0.03 to 0.87)	**74 fewer per 1,000** (from 85 fewer to 65 more)	⊕⊕◯◯ LOW
Any Adverse Effects Incidence (any duration, any dose) – Figure 5 of Manuscript											
5 interventions (n=3 studies)	randomised trials	not serious	not serious	not serious	serious [a]	none	96/725 (13.2%)	58/733 (7.9%)	**OR 2.03** (1.39 to 2.99)	**69 more per 1,000** (from 28 more to 125 more)	⊕⊕⊕◯ MODERATE
Heartburn Incidence (any duration, any dose) – Figure 19 of Online Supplementary Material 4											
3 interventions (n=3 studies)	randomised trials	not serious	not serious	not serious	very serious [a]	none	13/157 (8.3%)	6/155 (3.9%)	**OR 1.88** (0.68 to 5.18)	**32 more per 1,000** (from 12 fewer to 134 more)	⊕⊕◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference

Explanations

a. Wide CI; small sample size and small number of events.

b. 2/6 studies rated 'unclear' and 1/6 'high' for random sequence generation bias; 4/6 'unclear' and 1/6 'high' for allocation concealment bias.

c. Large variation in effect size; minimal overlap in confidence intervals; I2 high; P<0.05.

d. Moderately wide CI's

e. 5/5 studies rated 'unclear' risk of bias and 1/5 'high' for allocation concealment, however, unlikely to largely affect outcomes.

f. 1/4 studies rated 'unclear' and 1/4 studies rated 'high' for random sequence generation bias; 2/4 rated 'unclear' and 1/4 rated 'high' for allocation concealment bias.

g. 1/4 studies rated 'unclear' and 1/4 'high' for random sequence generation bias; 3/4 'unclear' and 1/4 'high' for allocation concealment bias.